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ORIGINAL CONTRIBUTIONS

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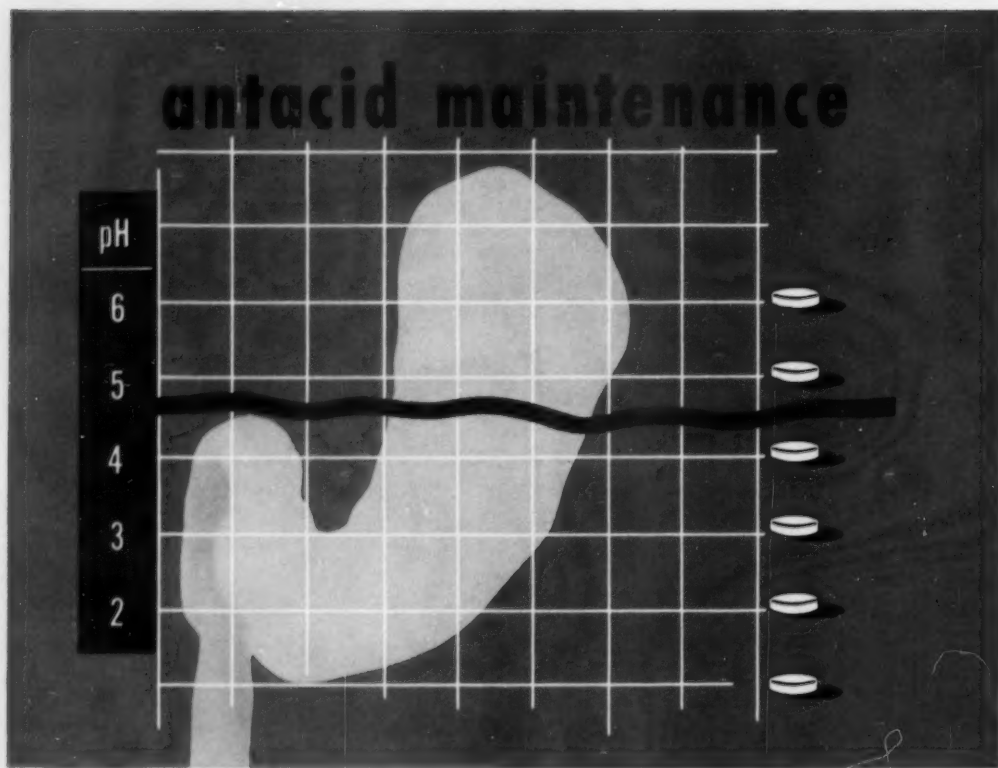
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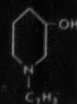
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1. Taggart, H. A.: Protein Metabolism in Relation to Nutritional Aspects of Medical Diseases, Pennsylvania M.J. 54:339 (1951).
2. Marquardt, G. H.; Cummins, G. M., and Fisher, C. I.: Blood Protein Replenishment in Treatment of Nephritic Edema, Quart. Bull. Northwestern Univ. M. School 26:140 (1952).
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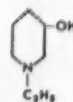
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DIFFICULTIES IN DIAGNOSIS OF ESOPHAGEAL CARCINOMA: FAILURE OF TRANSESOPHAGOSCOPIC BIOPSY

EDDY D. PALMER, LT. COL., M. C., Washington, D. C.

CARCINOMA OF the esophagus should be one of the more favorable gastrointestinal malignancies to diagnose and treat. Its presence may at times be suspected on routine physical examination by evaluation of the swallowing sounds, a rather small tumor often draws attention to itself early in this narrow and vulnerable tube, the esophagus is particularly accessible to both radiologic and endoscopic examination, and it is now technically possible to resect any part of the organ, with re-establishment of lumen continuity. Actually, carcinoma of the esophagus remains one of the most discouraging of all tumors. Perhaps the important reason is failure of overt symptoms to drive the patient to the doctor soon enough. But there is more to the problem than this, and one can predict that, when the day comes when preconsultation delay

has been eliminated, pretreatment delay in the doctor's hands will necessarily be increased considerably. If surgical extirpation continues to be the treatment of choice, this surely will be so, because esophagectomy is too mutilating a procedure to be contemplated unless the diagnosis of cancer is rather certain. The younger a tumor is, the more difficult the diagnosis will ordinarily be. Transesophagoscopy biopsy is by far the best way of proving the diagnosis at any stage, but there are difficulties involved in this technic late, as well as early, in the course of illness.

The purpose of this paper is to describe cases of esophageal carcinoma in which the first transesophagoscopy biopsy failed to establish the diagnosis and to discuss probable mechanisms.

OBSERVATIONS

In 13 of 100 personally observed cases of esophageal carcinoma the first biopsy failed to include tumor tissue. The X-ray films, esophagoscopy reports and

From the Gastroenterology Service, Walter Reed Army Hospital, Washington, D. C.

Submitted Oct. 15, 1954.

TABLE I

DATA ON 13 PATIENTS WHOSE FIRST BIOPSY FAILED TO SHOW CARCINOMA.
ALL NUMERALS (EXCEPT CASE DESIGNATIONS) REFER TO NUMBER OF
WEEKS FOLLOWING ONSET OF SYMPTOMS

Case	First sought help	Biopsy diagnosis	Location of tumor	Gross form of tumor	Operation	Outcome
1	12	14:esophagitis 16:carcinoma	Mid-esoph.	Infilt.	None:metast.	Died, 28
2	8	8:esophagitis 9:carcinoma	Aortic crossing	Infilt.	10:resection	Died, 11
3	8	8:normal 14:normal 15:carcinoma	Mid-esoph.	Fungat.	16:not resectable	Died, 32
4	4	6:esophagitis 8:esophagitis 9:esophagitis 15:esophagitis	Mid-esoph.	Infilt.	16:resection	Living, 24
5	4	5:normal 8:carcinoma	Mid-esoph.	Infilt.	None:invasion of trachea	Died, 32
6	1	1:esophagitis 5:carcinoma	Ampulla	Uleer	7:not resectable	Died, 29
7	13	13:normal 15:carcinoma	Ampulla	Fungat.	Refused	Died, 18
8	16	16:edema 17:carcinoma	Ampulla	Fungat.	19:resection	Died, 20
9	8	16:esophagitis 18:carcinoma	Distal third	Fungat.	Refused	Died, 58
10	20	28:normal 29:carcinoma	Mid-esoph.	Fungat.	29:resection	Died, 192
11	8	16:normal 17:normal	Aortic crossing	Infilt.	None:invasion of trachea	Died, 28
12	8	8:esophagitis 14:carcinoma	Mid-esoph.	Fungat.	None:invasion of trachea	Died, 22
13	1	11:normal 12:carcinoma	Mid-esoph.	Fungat.	13:not resectable	Died, 40

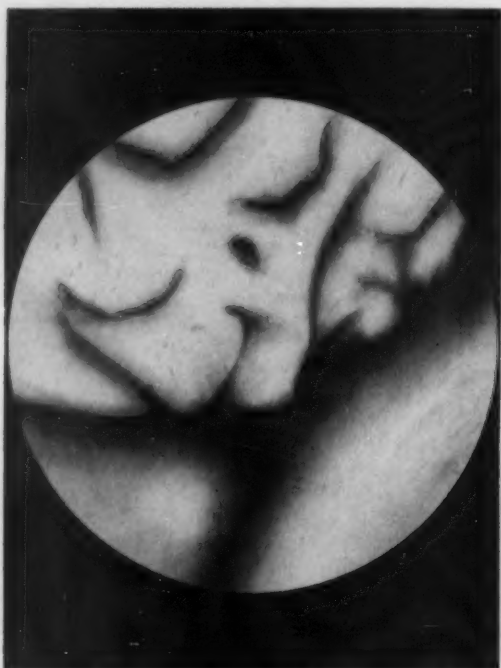


Fig. 1: Esophagoscopy view of orad portion of infiltrating carcinoma. Although appearances seemed to indicate that the tumor surface was exposed, only normal mucosa was obtained at biopsy.

sketches, biopsy specimens, and surgical and autopsy specimens were reviewed. Some details, with chronological information, are given in the table. In 11 instances the presence of an esophageal lesion suspicious of carcinoma was known at the time of the first esophagoscopy examination from the roentgenologic findings, and the two other lesions were encountered at esophagoscopy after normal roentgenologic study. In every case the first biopsy was taken deliberately from an area which to the esophagoscopist appeared to represent a lesion, probably carcinoma. The biopsy sites were selected under four-diameter esophagoscopy magnification. Pieces of tissue were routinely removed until the amount of bleeding precluded safe manipulation. An average of 3.3 tissue specimens per patient was removed at the initial examination.

In 10 cases biopsies removed at the second examination showed carcinoma. In two others the second biopsies failed to establish the diagnosis, and in another only esophagitis could be diagnosed after four examinations with biopsy.

The specimens removed at the first esophagoscopy examination showed only normal tissue in six instances, esophagitis in six, and subepithelial edema in one. The tumors had been located along various levels of the esophagus, and it could not be concluded that one level proved less fertile for biopsy than another. If the gross form of esophageal carcinoma is classified simply as infiltrative, fungating, ulcerous, or polypoid, the forms encountered among these 13 patients were infiltrating in five, fungating in seven, and ulcerous in one. The degree of obstruction was such



Fig. 2: Obstructing carcinoma. Composite concept of esophagoscopy appearances as they might have been, had it been possible to pass the esophagoscope beyond the tumor's orad limit. The normal esophageal mucosa has been rolled back (lower portion of drawing), to occlude the lumen and prevent direct access to the tumor.

that the esophagoscope could not be insinuated through and beyond the tumor in seven patients.

Examination of the gross tumor specimens, removed either at operation or autopsy, gave no explanation for biopsy failure in four cases. The grossly prominent orad limit of the tumor in each was free of normal epithelium and appeared to have been easily accessible to the biopsy forceps. The influence of continued growth on tumor configuration between time of biopsy and autopsy in two unresected cases could not be judged, but it had to be concluded that the forceps had simply been misdirected in these four patients.

The five infiltrating tumors had remained inacces-

sible because varying extents of their oral portions were entirely intramural, being covered with non-

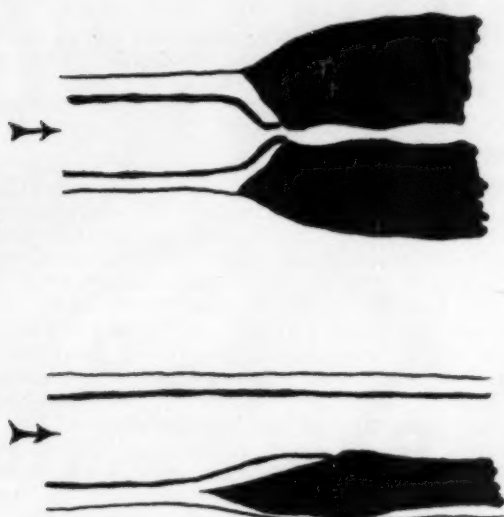


Fig. 3: Schematic representation of the two mechanical explanations for failure of the biopsy forceps to reach carcinomatous tissue.

neoplastic mucosa. The esophagoscopist had considered these portions to be cancerous and had not been able to recognize the nature of the overlying tissue. The mucosa in each instance had been elevated, uneven, opaque, and hard (Fig. 1), seemingly the proper area for a fruitful biopsy.

The other four cases were instances of high-grade obstruction, and the possible failure of biopsy was recognized at the time of esophagoscopy. The mucosa—in these patients recognized as noncancerous—had been pushed back by encircling tumor (Fig. 2). The esophagoscopic diagnosis of cancer was made on the basis of the hardness and immobility of the tumor. Biopsies were taken blindly by passing the forceps into the tumor lumen and taking several bites of whatever could be caught. In most such cases tumor tissue can be recovered, but in these four only normal or inflamed mucosa was found (Fig. 3).

CONCLUSIONS

It is to be expected that in a portion of cases of esophageal carcinoma several biopsy attempts will be necessary before a tissue diagnosis can be established. Three important explanations for biopsy failure are intramural position of some infiltrating tumors, obstruction which precludes access to exposed tumor tissue, and simple misdirection of the forceps.

AMBULATORY CONTINUOUS DRIP METHOD IN THE TREATMENT OF PEPTIC ULCER

F. STEIGMANN, M.D. AND E. GOLDBERG, M.D., Chicago, Ill.

THE IMPORTANCE of excessive acidity in the genesis and persistence of peptic ulceration is agreed upon by most workers in this field, although there is some difference of opinion as to how this increased acidity produces its effect. The statements of Schwartz (1), Sippy (2), and Palmer and his associates (3) that control of gastric acidity is mandatory in the relief of pain, as well as the promotion of healing in peptic ulceration, have been confirmed by numerous clinical observations in the past half century.

At present, gastric acidity can be controlled medically in two ways. One way is to prevent or depress the formation of hydrochloric acid, the other, is to neutralize the acid already present in the stomach. While many new substances have been produced in recent years to suppress gastric acid secretion, none of them is, as yet, sufficiently powerful to prevent acid formation throughout a 24 hour period without producing too many undesirable side effects. Substances which neutralize the already formed acid gastric juice—antacids—are, therefore, still needed for the control of acidity in patients with peptic ulcer.

From the Department of Internal Medicine and the Gastro-intestinal Clinic of the Cook County Hospital, Chicago, Illinois.

This study was aided in part by a grant from the Horlicks Corporation, Racine, Wisconsin.

MARCH, 1955

The goal of antacid therapy is continuous effective neutralization of free acid in the stomach, consequently the elimination of peptic activity of the gastric juice. The effect of antacid therapy occurs during, and for only a short time after, the period of administration. The length of this effective period depends on the type of antacid, i.e., its chemical and physical characteristics, the quantity taken, the frequency of administration and the mode of ingestion.

Numerous observations have indicated that for a complete neutralization of gastric acidity, most of the antacids must be taken at frequent intervals (4). The success of the original Sippy treatment depended largely on continuous neutralization of the free acid by frequent ingestion of alkalies alternating with milk and cream. Later on, Winkelstein (5) introduced continuous intragastric drip therapy as another method for controlling gastric acidity in patients unable to take frequent medication, e.g., during the night.

A survey of presently used antacids indicated that almost all of them, whether taken as powders, liquids or tablets have a short antacid effect in the stomach as measured by fractional gastric analyses (6). Most of the antacids tested controlled free acidity for not more than 15 to 60 minutes, regardless of the form in which the medication was administered.

In view of the above, it is plausible to believe that patients who take 1-2 tablets, or 1-2 teaspoonfuls of

some antacid after meals have a controlled gastric acidity for only a short time. Since most patients are loath to take medications too frequently, their gastric acidity is, accordingly, neutralized only part of the time. In many patients, this is inconsequential. In others, ulcer symptoms are not sufficiently controlled by intermittent antacid medication because these patients need prolonged and constant neutralization of their gastric secretions. Hospitalized patients can be adequately treated with a regular milk-antacid regimen or with a continuous intragastric drip of a milk-medication mixture. However, with ambulatory and working patients neither of these procedures is possible.

Recently, a new antacid tablet has been added to the armamentarium of the practitioner for the treatment of peptic ulcer. This tablet consists of a mixture of antacids and milk powder, prepared in such a way as not to be chewed or swallowed as a whole, but to be kept between the gums and the cheek and left to dissolve on its own. The presence of this tablet in the buccal cavity stimulates salivation so that the patient continuously swallows saliva containing portions of antacids and powder contained in the tablet.

These antacid tablets* contain solids from whole milk, combined with dextran and maltose, magnesium trisilicate, magnesium oxide, calcium carbonate, magnesium carbonate and peppermint oil. They are approximately the size of a quarter, and only slightly thicker, so that they can be kept in the mouth, between the gums and cheek, without discomfort and without interfering with speech. The tablets are so prepared that they dissolve slowly—over a period of 25-60 minutes.

Since this method of an ambulatory continuous drip therapy appeared promising in the therapy of some peptic ulcer patients, a study was planned for testing the value of these antacid tablets both from the acid neutralization and therapeutic point of view. This paper represents a report of our observations in a comparatively small group of patients during a period of over one year.

MATERIAL AND METHOD

Gastric Secretory Study

Patients with the proven diagnosis of peptic ulcer—duodenal or gastric—were tested for the effect of these antacid tablets on the acidity of the histamine stimulated stomach. The following procedure was used: Fasting subjects—gastric or duodenal ulcer patients—were intubated with a Levine tube and their gastric contents were completely evacuated. Thereafter, gastric aspiration was done at 15 minute intervals until three additional samples were obtained. After the fourth sample was aspirated, the subjects were given 0.1 mgm. of histamine per 10 kilo weight, and the aspirations were continued every 15 minutes for another 75 minutes. On the next day, this technique was repeated. However, at this time, the subjects were given the tablet simultaneously with the histamine injection. Aspirations were continued as on the previous days, while the patients continued to swallow, intermittently and naturally, (usual swallow-

ing intervals) saliva mixed with the dissolved products of the tablet. A group of patients was tested with one, another group with two and a third group with three tablets.

The difference in the height of the curves on the two days was considered to be the degree of acid neutralization by the antacid substance.

Clinical Study

Patients suffering from gastro-duodenal ulcer (5 gastric and 30 duodenal ulcers) or hypertrophic gastritis were used for this study. The diagnosis was based on history, routine physical examination, roentgenological studies of the upper gastro-intestinal tract including the gall bladder, and secretory studies and gastroscopy. The patients ranged from 17 to 70 years of age. There were 14 women in the series. The patients in this series gave a history that ranged from three weeks to twenty years—the average being about eight years. Of the 30 duodenal ulcer cases 2 had previously perforated; 2 had bleeding episodes and 5 showed penetrations (large craters). Of the 5 cases with gastric ulcer 1 had antral spasm with a moderate three hour residue of barium in the stomach and 1 had, in addition, a duodenal ulcer and cardiospasm.

Most of the patients in this series (90%) had previously been on antacids, such as Sippy powder, aluminum gels, magnesium trisilicate, calcium carbonate or gastric mucin, and some had been on diet therapy alone. The remainder were on no particular regimen.

The patients in this series have to be divided into two groups. The first group includes 27 patients, and is composed of previously treated patients who started on the new therapy because of an exacerbation or recurrence of symptoms. The second group (19 cases) consists of patients who were designated intractable because they did not respond to a previously instituted medical regimen. Some of the patients in the latter group had been on alkali and various aluminum gel mixtures in addition to diet, sedatives and antispasmodics, but continued to have symptoms to such an extent that new therapeutic agents were indicated. The 5 duodenal ulcers with penetration fell into this latter group. In 2 of these, severe backache disappeared after institution of this new regimen.

All patients were put on ambulatory medical management, with the exception of 4 who were in the hospital when the treatment was started. Of the latter, one had both a gastric and duodenal ulcer and cardiospasm, one a penetrating duodenal ulcer, one a chronic duodenal ulcer, and one hypertrophic gastritis and duodenal ulcer.

The hospital patients were put on a bland diet, with milk and cream at mealtime and between meals. No night feedings were permitted. All of the patients were given the tablets at their bedside with the instruction to keep one tablet in their mouth at all times except while eating. Antispasmodics and sedatives were given by the nurse four times daily.

The ambulatory patients were advised to keep a tablet in their mouth at all times during their waking hours, except while eating. In every instance the pa-

*Nulacin, manufactured by Horlicks Corporation, Racine, Wisconsin.

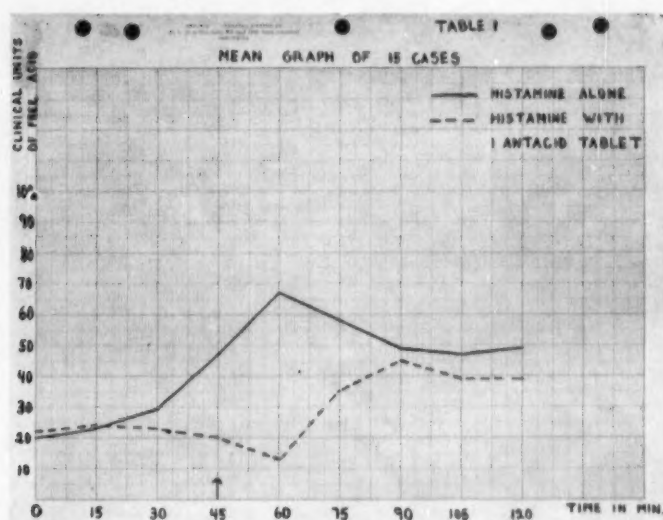


TABLE I

tient was advised not to chew or swallow the tablet and not to move it from side to side. Antispasmodics and sedatives were ordered three times daily and at bedtime. All the patients were advised against alcoholic beverages, coffee and smoking. Whenever indicated, psychiatric consultation was advised and utilized. Most patients took 12-14 tablets daily, although some took as many as twenty for the first few days.

X-rays were taken before the treatment was begun and at various intervals during therapy. The patients with gastric ulcer were x-rayed after 2 weeks and again after 4 weeks.

Gastroscopic examination was not done routinely in the duodenal ulcer group, except when gastric pathology was suspected. In the gastric ulcer group,

however, gastroscopic examination was done if at all possible, and repeated at least once in the first four weeks of treatment.

RESULTS

Secretory

Following the "taking" of the tablet, there was noted a decrease of the amount of free acid obtained after histamine stimulation. The gastric acidity dropped for variable lengths of time and for variable degrees while the patient had the tablet in his mouth. After the tablet was completely dissolved the acidity showed some rise to its former levels— but did not reach the acidity height of the control day. In some patients there was a rise of the acidity after a short-lasting fall, just as in cases treated with other types

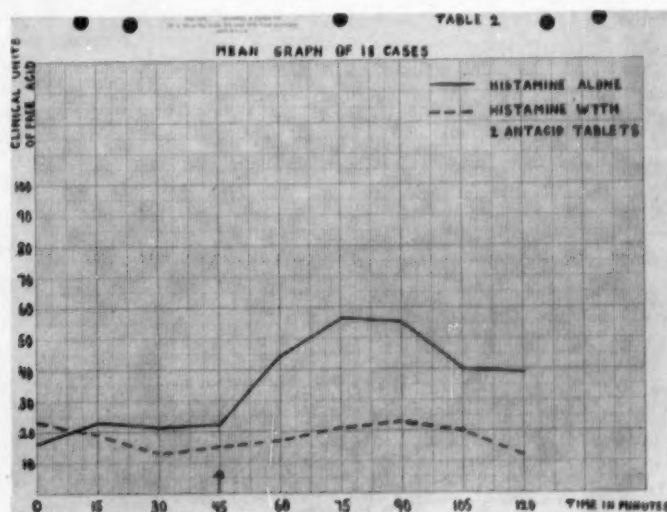


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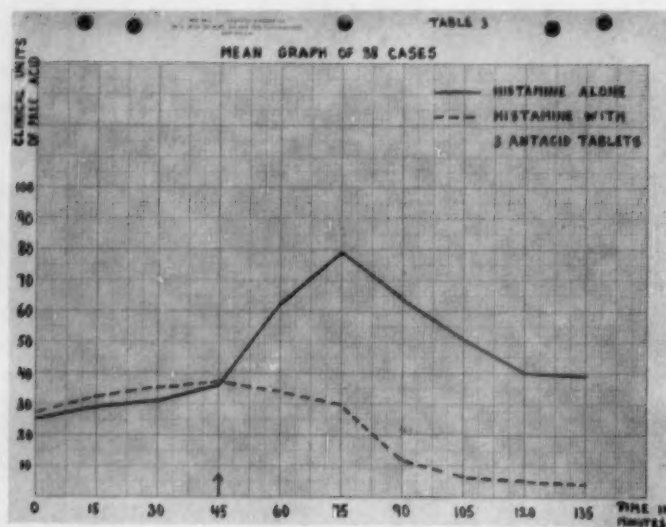


TABLE III

of antacids which were either swallowed or chewed. Most of them, however, showed a prolonged decrease as can be seen from the mean curve (Graph 1).

After taking one tablet, and following it with a second one, when the first tablet was dissolved the gastric acidity was depressed for a longer time, and there were hardly any returns to the previous day levels (Graph 2). If three tablets were taken in succession, the gastric acidity remained depressed during the entire observation period reaching an anacidity level for the final 15-30 minutes of the observation (Graph 3).

Clinical Study

In almost all the patients who were started on a regimen of continuous antacid therapy by slow dissolution of the tablets held in the mouth, gastric symptoms improved. In some the pain was relieved promptly, while in others some pain was experienced intermittently at first. The taking of a tablet at bedtime prevented previously occurring night pain in some patients. As the patients felt less pain they decreased the number of tablets per day. The decrease was reached mainly by using each tablet for a longer time, i.e. by keeping the tablet quite still and not moving it. As the patients became further symptom free they developed their own system for control of their symptoms, e.g. taking 1-3 tablets in succession, starting one-half to one hour after meals, etc.

Of the patients starting this therapy, 10 were under observation for less than 3 months, the patients not returning for checkup or additional medication anywhere from 4-12 weeks later. All of these, however, reported feeling improved when last seen. Of the remainder, one was under observation for 5 months, 3 for 6, 5 for 7, 7 for 8, 10 for 9, 2 for 11, 2 for 12, 2 for 13, 3 for 14 and 1 for 15 months.

All of the patients improved initially, some of them, however, discontinued therapy later for various rea-

sons—in most instances because the patient felt well enough to do without medication. Some of the patients who have continued for months under observation have taken only up to 6 tablets daily in the later part of the observation period and they, too, at times, did not take any medication for days. Only a small number (10 patients) have continued to take 10-12 tablets daily for up to 8 months, mainly because they hoped that this would prevent future recurrences.

Untoward effects

Except for 5 cases, all patients took the medication without complaints. One patient refused the tablets after 2 weeks because of the sweetish taste which made him nauseated, one because they hurt his teeth and one because they made him "gassy" and gave him a burning sensation in his throat and a bad taste in his mouth. There were no complaints of constipation or diarrhea, although several patients felt that their stools were softer and had a better consistency while they were taking the tablets. Two patients discontinued the tablets after 2 and 5 months, respectively, because they disliked the sweet taste. Two patients stopped taking the tablets after a short time, 7 and 10 days respectively, because apparently they experienced no relief of their symptoms.

DISCUSSION

Our experiences with this new method of antacid therapy seem to confirm the initial reports on this substance from the continent (7a,b,c). Relief from epigastric distress was obtained by the majority of patients within a short time, probably due to a more complete neutralization of gastric acidity as one might hypothesize from the results of the secretory studies. There seemed to be little objection to the keeping of these antacid tablets in the mouth, or to the frequency with which they had to be taken. As their symptoms improved, patients began to cut down on the number of tablets taken per 24 hours. It seems that the main

indication for this new antacid tablet is in patients with acute ulcer exacerbation and its associated severe pain. In these latter patients, the constant swallowing of a saliva mixed with alkali seems to greatly alleviate the upper abdominal distress. It is in this type of patient, too, that "ambulatory drip therapy" gets its greatest rewards. It appeared that the patients preferred putting a tablet into their mouth at frequent intervals to swallowing tablets or taking powders or even liquid antacids at regular intervals.

It is hard to evaluate why some patients had sensations of a bad taste from these tablets early and some only after prolonged use of the tablets. However, since only comparatively few patients complained of this, it is possible that the incidence of this untoward effect might be less in a larger series of cases. The lack of any bowel disturbance—constipation or diarrhea—in these patients is another factor in favor of ulcer therapy with this new antacid tablet.

SUMMARY

In 46 patients the effects of a new orally dissolving antacid tablet were observed for varying lengths of time.

A good initial response was obtained in almost all of the patients; only minor side effects were noted in the patients taking this antacid.

This mode of administering antacid "ambulatory

drip therapy" seems to offer a new highly effective approach in the treatment of patients with peptic ulcer.

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NEEDLE LIVER BIOPSY: FOR THE DIAGNOSIS OF NEOPLASM

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NEEDLE BIOPSY of the liver, when properly performed, should cause the patient little discomfort and provide a reasonably informative specimen of liver tissue. The use of this technique has often spared the patient unnecessary laparotomy in cases of neoplasm.

Liver biopsy has been performed in twenty-eight patients with malignant neoplasm of the liver during the past five years without a serious complication. The diagnosis has been verified by follow-up, operation, biopsy or necropsy. All of the biopsies were performed with the Vim-Silverman needle. The technique has been reported earlier by Kumpe (1). The primary tumor sites are listed in Table I.

Twenty-six biopsies were made using an anterior subcostal approach over the enlarged right or left lobe of the liver; two biopsies were made through an intercostal approach in the anterior axillary line. All biopsies were done at the patient's bedside.

Liver biopsy showed the presence of neoplasm in 23 of 28 cases. The first biopsy was adequate in each of the 23 patients whose biopsies were positive for

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TABLE I

PRIMARY SITE OF THE TUMOR (28 CASES)

	Number of Cases
Breast	5
Stomach	5
Site undetermined	4
Colon	2
Arm (neurogenic sarcoma)	2
Liver	2
Pancreas	1
Thyroid	1
Lymphosarcoma	1
Ovary	1
Hodgkins	1
Esophagus	1
Uterus	1
Eye (melano-sarcoma)	1

neoplasm. The histologic nature of the lesion is listed in Table II. Tumor was not found in five biopsies although liver tissue was obtained; these showed peri-

TABLE II

HISTOLOGIC NATURE OF THE BIOPSY SPECIMENS
(23 CASES)

	Number of Cases
Metastatic Adenocarcinoma	10
Metastatic Carcinoma, unclassified	7
Neurogenic Sarcoma	2
Metastatic Carcinoma (squamous-like)	1
Primary Carcinoma of the Liver (Hepatoma)	1
Lymphosarcoma	1
Metastatic melanocarcinoma	1

cholangitis in one, hemochromatosis in one, and normal liver in three.

All, but one, of the 28 patients had enlarged livers on physical examination. Among these 28 cases a positive diagnosis was obtained in 22 of 26 using the anterior subcostal approach and one of two using the intercostal approach. The value of liver biopsy in the diagnosis of neoplasm of the liver is indicated in Table III.

The clinical impression of malignancy was con-

TABLE III

VALUE OF LIVER BIOPSY IN THE DIAGNOSIS OF
NEOPLASM OF THE LIVER

	Number of Cases
Confirmed the clinical diagnosis	21
Revealed the correct diagnosis	2
Failed to demonstrate neoplasm	5

EFFECTS OF ANTICHOLINERGIC COMPOUND 14045 (ELORINE
SULFATE) ON GASTRO-INTESTINAL MOTILITY IN THE HUMAN

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THIS IS a report of a preliminary study of the experimental effectiveness of a new anticholinergic, compound 14045 (1-Cyclohexyl-1-phenyl-3-pyrrolidino-1-propanol methylsulfate), in suppressing gastro-intestinal motility in the human.

The natural crude alkaloids of the belladonna plant and its purified derivative atropine have been employed effectively for many years in gastro-intestinal disorders. Their ability to block parasympathetic impulses have made them useful in controlling the symptomatology provoked by hypermotile and spastic states. Unfortunately their action is not restricted to the smooth muscle of the gastrointestinal tract (1). These agents also paralyze the ciliary muscles of the

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TABLE IV

CASES IN WHICH LIVER BIOPSY CHANGED THE
CLINICAL DIAGNOSIS

Clinical Diagnosis	Biopsy Diagnosis
1. Chronic hepatitis	Metastatic Adenocarcinoma
2. Pancreatitis with obstructive jaundice	Metastatic Adenocarcinoma

firmed in twenty-one patients by the biopsy. In two patients, one of whom did not have hepatomegaly, the biopsy established the correct diagnosis, Table IV.

The most important objection to needle liver biopsy is the inability to demonstrate focal or widely separated hepatic lesions. Yet the number of positive biopsies (82%) in this series is high and is comparable to the experience of Safdi (2), Kleckner (3), and Ward (4). Since neoplastic disease of the liver is difficult to diagnose clinically or by liver function studies, needle liver biopsy should be of considerable aid in establishing the correct diagnosis.

SUMMARY

1. Needle liver biopsy revealed the presence of hepatic neoplasm in 23 of 28 patients with neoplasm of the liver.

2. The biopsy confirmed the clinical impression of malignancy in 21 of 23 cases. In two cases the biopsy changed an incorrect to correct clinical diagnosis.

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lens and the sphincter muscles of the iris resulting in cycloplegia and mydriasis. They similarly attack parasympathetic influences on the secretory function of the salivary glands producing troublesome xerostomia. In therapeutic doses they block parasympathetic cardio-inhibitory fibers inducing unpleasant tachycardia.

In an attempt to circumvent these side effects numerous synthetic anticholinergic compounds have been derived. It had been hoped that these new drugs would permit a more selective or target blockade of the cholinergic nerves mediating excessive gastro-intestinal function. Etamon (2, 3), a quaternary ammonium compound and one of the earlier drugs studied, was found to have a powerful effect on the cardio-vascular apparatus limiting its clinical use in gastro-intestinal disorders. Other blocking agents that have come to the fore in the last few years include Banthine (4, 5), Hexamethonium (6), Bentyl (7, 8), and Prantal (9). All of the agents have been shown to be

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good inhibitors of gastro-intestinal motility. However, in effective doses, they often produce unpleasant side reactions.

For the past year and a half we have been concerned with the problem of screening an effective anticholinergic agent from a large series of newly synthesized compounds. Two of these drugs, WIN 4369 (Monodral) (10, 11, 12) and Compound 14045 (Elorine Sulfate, Tricoloid), have been particularly successful as cholinergic blocking agents. The latter drug has also recently been studied by Kirshner and Palmer (13) and found to have appreciable gastric antisecretory effects. The substance of this report deals with Compound 14045 and its effectiveness in inhibiting motility of major segments of the gastro-intestinal tract. The frequency, severity and type of side reactions are described and compared with its usefulness as a suppressor of gastro-intestinal motility.

Compound 14045, chemically, is 1-Cyclohexyl-1-phenyl-3-pyrrolidino-1-propanol methylsulfate. In anaesthetized dogs (14), intravenous doses of 0.02 to 1.0 mgms. per kg. block the hypotensive effect and augmentation of duodenal motility induced by intravenous urecholine. In anaesthetized dogs with Thiry type fistulas of the jejunum and ileum, Compound 14045 also counteracts the stimulating effects of urecholine. Toxicity studies in animals have shown that the drug is relatively non-toxic (14). The acute intravenous toxicity in mice (LD_{50}) is 12.7 ± 0.4 mg. per kg. while orally the LD_{50} is 554 ± 30.5 mg. per kg. The drug seems to be safe after chronic administration to animals. Rats were able to tolerate 0.5 % in the diet for one month without weight loss or evidence of visceral damage (14).

METHOD

The balloon-kymographic method was employed to record the drug induced motility changes. From the antrum and duodenum simultaneous kymographic records were obtained with the aid of a double lumen Miller-Abbott tube and latex balloons attached in tandem to each channel. Nine subjects were used in this study. Following oral intubation, the tube was guided and placed into position under fluoroscopic control. For sigmoidal intubation a latex balloon attached to an 18 French rubber tube was introduced through a sigmoidoscope. The recording apparatus employed was a modification of one previously described by Kern and co-workers (15). The volume-pressure changes caused by gastro-intestinal contractions were registered by ink writers carried on balsam wood floats in large glass U-tube water manometers. This recording system was connected with the intra-luminal balloons by means of rubber tubes. A kymograph with a 60 inch extension permitted simultaneous registration of motility from different segments of the gastro-intestinal tract at controlled speeds of 1 cm./minute. Motility patterns were obtained under conditions of standard stimulation, i.e. inflation of the intra-luminal balloon with 50 c.c. of air. In some subjects the drug induced inhibition was challenged by additional distention with 50 c.c. of air or the subcutaneous injection of 5 mgms. of urecholine.

The dose of Compound 14045 employed in all experiments was 100 mgms. A fasting tracing of 10 to 20 minutes was obtained. The subject was then given a placebo sugar capsule and an additional 20 to 45 minutes of tracing recorded. The test drug was then administered orally with a small amount of water.

TABLE I
COMPOUND 14045 (ELORINE SULFATE): EFFECTS OF 100 MGM.
ORAL DOSES ON GASTRO-INTESTINAL MOTILITY

Case	Site of Balloon	Observed Action of Drug		Degree of Suppressed Motility	Effect of Challenging Agents (Balloon Distention Urecholine)
		Onset	Duration		
1. P. C.	Antrum	15 min.	96 min.	{ 36 min.—marked 60 min.—moderate
2. J. N.	Antrum	18 min.	120 min.	marked
	Desc. Duod.	20 min.	98 min.	{ 38 min.—marked 60 min.—moderate	
3. R. K.	Antrum	18 min.	150 min.	marked
	Desc. Duod.	18 min.	150 min.	marked	
4. L. O.	Antrum	20 min.	90 min.	marked	none
	Desc. Duod.	22 min.	90 min.	{ 40 min.—marked 50 min.—moderate	mild
5. E. H.	Antrum	16 min.	122 min.	marked
	Desc. Duod.	19 min.	116 min.	marked	
6. P. L.	Antrum	22 min.	100 min.	{ 35 min.—marked 65 min.—mild	moderate
7. A. B.	Sigmoid	a) 17 min.	60 min.	marked
		b) 19 min.	60 min.	marked	
8. I. K.	Sigmoid	16 min.	60 min.	{ 30 min.—marked 30 min.—none	marked
9. A. K.	Sigmoid	17 min.	75 min.	marked

The patterns obtained during these 30 to 65 minutes of pre-drug intervals were compared with the post-drug motility patterns. By simple inspection drug-induced suppression of motility was recorded as mild, moderate or marked. No attempt was made to more precisely quantitate wave size, frequency or area since the balloon-kymographic method of recording gastrointestinal motility is recognized to be relatively crude.

RESULTS

The effect of the drug on antral motility was studied in six subjects. Inhibition usually appeared 18 to 20 minutes after drug ingestion. In two of the six (J.N., E.H.), as noted in Table 1, complete suppression of motility lasted two hours. In one subject (R.K.) marked inhibition persisted for 60 minutes followed by two short periods of activity in the second hour. This record is reproduced in Figure 1. In another individual (P.C.) inhibition lasted for 36 minutes followed by only a mild return of motility which was observed for an additional 60 minutes. In a fifth subject (L.O.) the cholinergic blocking effect of the drug was challenged by additional air distention. Motility reappeared but not to the degree of the pre-drug period.

In four subjects the effects on the descending duodenum were studied simultaneously with some of the antral records described above. Inhibition was almost

complete for two hours in two of these (E. H., R. K.). The record of one of these (R. K.) is reproduced in Figure 2 and shows only small and infrequent "S" waves following drug ingestion. In another patient (J. N.) complete suppression of motility for 38 minutes was followed by only a minimal return of phasic activity for 60 minutes. In the fourth subject (L. O.) the drug-induced inhibition was challenged by additional air distention and urecholine. Phasic activity returned following these challenging agents but it was not as great as during the pre-drug period.

The effect of Compound 14045 on sigmoidal activity was studied in three subjects. In the first patient (A.B.) two separate studies were performed employing 50 and 100 c.c. of air distention. On each occasion the drug effects were similar. Marked inhibition of sigmoidal activity occurred 10 to 15 minutes after drug ingestion and persisted for an observed period of one hour. In another patient (I.K.) the drug-induced sigmoidal inhibition was effectively challenged by urecholine. There was a prompt return of pre-existing phasic activity. The third subject's record is shown in Figure 3 (A.K.) and demonstrates marked inhibition of motility for more than one hour.

SIDE EFFECTS

The side effects of the drug were evaluated by observing the degree of change in pulse rate, dryness of the mouth, pupillary dilatation and accommodation.

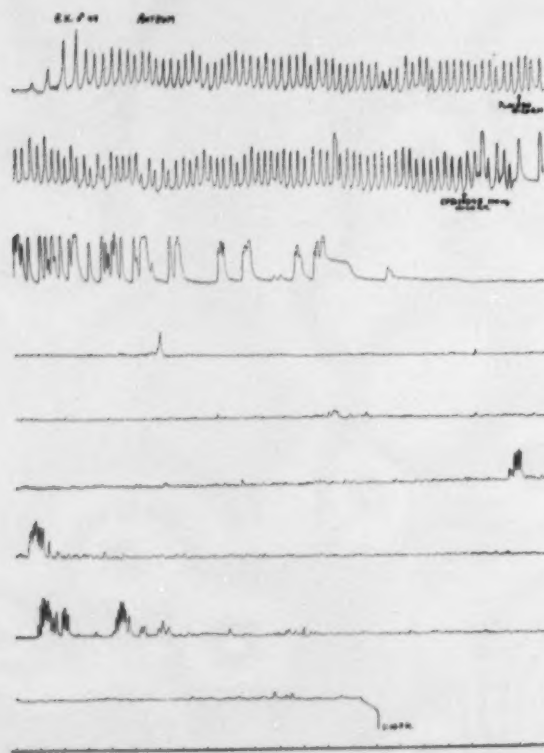


Fig. 1: Effect of Compound 14045 (Elorine Sulfate), 100 mgm. oral dose, on antral motility. Note almost complete suppression of motility except for brief periods of activity in the second hour.

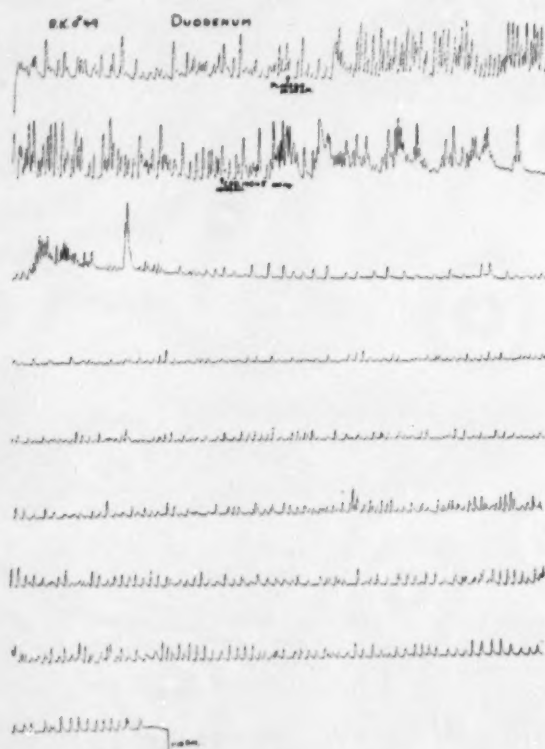


Fig. 2: Effect of Compound 14045 (Elorine Sulfate), 100 mgm. oral dose, on duodenal motility. Note the marked suppression of motility with persistence of small "S" waves.

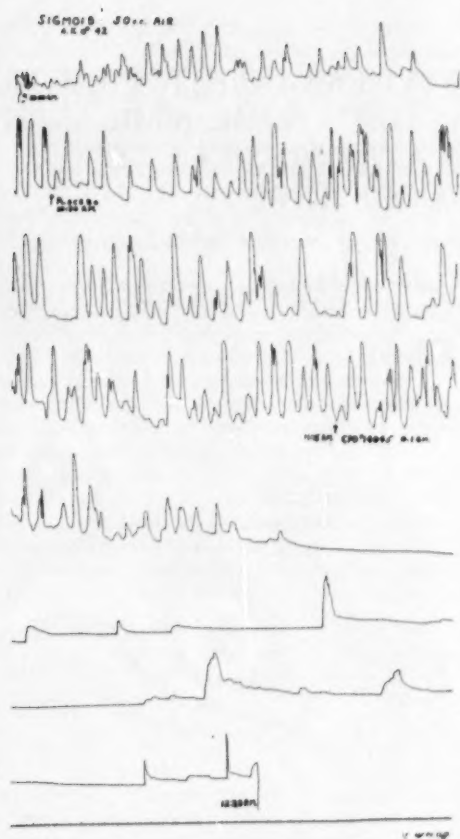


Fig. 3: Effect of Compound 14045 (Elorine Sulfate), 100 mgm. oral dose, on sigmoidal motility. Note marked suppression of sigmoidal activity.

During the first hour after drug ingestion none of these effects were observed. In three patients dryness of the mouth was noted. It was present to a marked degree in only one and occurred two hours after drug ingestion. Mydriatic effects were minimal in these same three patients. A rise in pulse rate of 20 to 30 beats per minute over the pre-drug period, but never exceeding a pulse rate of 100 per minute was only noted in these three patients. Loss of accommodation, as tested by the ability to read a printed page, was minimal in one of these three. In another, cycloplegia was present to an uncomfortable degree six hours after the drug had been administered. Thus, side effects following 100 mgm. doses of the drug were totally absent in six patients, minimal in two and marked in one patient.

SUMMARY AND CONCLUSION

Compound 14045 (Elorine Sulfate; 1-Cyclohexyl-1-phenyl-3-pyrrolidino-1-propanol methylsulfate) appears to be an effective anticholinergic compound. The

oral administration of 100 mgm. doses in nine human subjects suppressed gastro-intestinal motility as indicated by balloon-kymographic tracings taken from the gastric antrum, the duodenum, and the sigmoid. Side effects were minimal. These preliminary results suggest that the drug merits further experimental and clinical study.

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AMINOPTERIN TOXICITY REVERSAL BY A HEMOPOIETIC FRACTION OF MICROBIAL "ANIMAL PROTEIN FACTOR": SOME SIMILARITIES OF STREPTOMYCES FERMENTATION RESIDUE TO PITUITARY ERYTHROPOIETIN

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SINCE THE original reports (1) of their utility in human leukoblastic disease, the dried, spent liquors from various antibiotic-producing streptomyces species fermentations have had broad, if desultory therapeutic trial in this country and abroad. The first of such residues, that from the ordinary streptomycin producer, streptomyces griseus, was introduced to commerce as a swine and poultry feed supplement under the designation of "animal protein factor" (APF) on the basis of its high B₁₂ content, the latter being assumed to be that constituent responsible for the biologic superiority of animal, over plant protein in the diet of non-ruminants including humans. This presumption has since gone by the boards and the nutritional virtues of APF's were later ascribed to the traces of antibiotic which they contained (2).

But neither the nutritional or (other) therapeutic effects of streptomyces fermentation administration appear to be completely forthcoming from purified B₁₂, purified streptomyces-derived antibiotic (the "mycins") or their combination. An example resides in the pronounced ability of commercial, streptomyces-APF to reverse the toxicity of aminopterin in weanling rats which (with the single exception to be taken in the discursive portion of this report) has no quantitative parallel. Aminopterin poisoned rats not only survive, but actually thrive when fed crude streptomyces broth. The reversal itself, let alone its surpassal, is not accounted for by the small pteroylglutamates (folic and folinic acid) content of the broth, nor that of any known constituent. Evidently unknown but highly active constituents are present.

Recent revival of interest in such constituents has attended the vigorous screening procedures to which the thousands of different streptomyces strains are now being subjected. A variety of "antivirals" as well as "antineoplastic" agents (including the widely-publicized and just as widely disappointing azaserine) are found to be streptomyces fermentation elaborates. Waksman (3) has popularized the work of the Hackmann-Shulte group on palliation of Hodgkin's disease with an actinomycin-producing, streptomyces filtrate, a result previously obtained by us with any antibiotic-producing streptomyces liquor (4, 5). The laboratory experimental demonstration of "antineoplastic" properties for these liquors was reported as early as 1949 by Rokujo and his coworkers, collaborating with Umezawa's group (6) and the latter has extended assignment of these properties to a large number of streptomyces species.

But perhaps the most remarkable emergence on constituency of microbially derived APF's was the demonstration by Nelson, O'Connell and Haines that

they contained a biologically active material indistinguishable from pituitary ACTH (7). These authors, pointing out previous detection of a "corticotropin" in a nonpituitary connection, the placenta, did elicit a priorly unknown non-mammalian animal source of corticotropin; the fish meal which has also had extensive use as a poultry feed "animal protein factor" supplement. They extended the prior demonstration by Takeda et al (8) of an ACTH-like material in *Ps. fluorescens* to the latter's presence in other bacteria which might be commensally in the human intestinal tract; a lactobacillus, a pigmented strain of *s. marsecens* ("B. prodigiosus"), *B. subtilis* and an *E. coli* strain.

This important revelation was thought at first to be unconnected with the fact that feedings of streptomyces APF or streptomyces antibiotics, or the intestinal flora reversion produced by the latter had been repeatedly followed by "adrenocorticomimetic effects" (9). These, however, could not reasonably be ascribed to microbial corticotropin, either that of ingested APF or autochthonously from intestinal bacteria since ACTH is supposedly orally ineffective because as a peptide it would most certainly be degraded by enteral proteases. Still, this a priori reasoning overlooked the facts that ACTH is rather resistant to both peptic and tryptic digestion and, that if a predominantly saccharolytic intestinal flora were present, the lower bowel protease content would be curtailed. On oral administration of either pituitary or streptomyces corticotropin these were found to exert a systemic effect—theory to the contrary notwithstanding so that Coren and Barnard (10) by calculation around its magnitude suggested that an appropriate intestinal flora may not only contribute to the corticotropic milieu of the host, but constitute the main source of the adenohypophysis' precursor.

The presence of an orally active corticotropin in it, does not however exhaust the list of active constituents of APF (11). It produces a better hematologic response in leukemic patients or those with radiation anemia than does ACTH and furthermore it has been found effective in some patients who are refractory to corticotherapy. ACTH administration does not promote growth of aminopterin-poisoned weanling rats and its reversal of the poisoning is equivocal. Evidently characterization of possible additional factors is in order.

This report is based on the systemic aminopterin-reversing properties of a particular fraction of lot ER, Pfizer's Bicon, a dried broth from streptomyces griseus marketed as an animal-feed supplement and in current experimental therapeutic use. The particular fraction, SGE, is an acid eluate of a charcoal adsorbate of ER (12). Spectrophotometric examination of SGE fails

*From the Professional Pathological Laboratories, 1 W. 34 Street.

to reveal pteroylglutamates, cobalamine, porphyrins or inorganic cobalt. Mycin antibiotic is undemonstrable by bacterial inhibition tests. Whereas a trace of 11-oxy steroid may be present in original ER, the method of preparation of SGE precludes its presence in the latter. In other words, it appears to be devoid of any single constituent having variously been reported to confer protection against aminopterin in the rat. Still, in four consecutive series it proved to be one of the most active protectants encountered.

EXPERIMENTAL

Testing for aminopterin toxicity and its reversal was conducted in the manner previously outlined (13). Twenty to thirty day old weanling female rats were segregated into groups of 6 to a wire-screen bottomed, metabolism cage (to prevent coprophagy which may confer some protection). Fresh homogenized milk incorporating the test materials was allowed each group in 100 cc. daily quotas for the first two weeks and 150 cc. for the third week. Enriched white bread was given ad libitum. From milk consumption tabulation it was calculated that during the first two weeks each rat in all except the control group received an average of 8 gammas of aminopterin daily and during the third week the average was 12 gammas daily in "protected" groups. In the group receiving only aminopterin, this amount was allowed but evidently not consumed; the food intake of "unprotected" animals usually dropping sharply during the third week at this dosage level.

Animal weights were recorded at the outset and each week thereafter. Following the 4th weighing, surviving animals were sacrificed, autopsied and blood and bone marrow examination performed.

RESULTS

In the first three series, employing 2 milligrams of SGE per rat per day, the degree of protection obtained and the condition of the animals at the conclusion of the experiment were phenomenal. Since such series may successively go awry for a variety of reasons, most of which are still unelucidated (viz., there is still no agreement on the factuality of cortisone or tetracyclin antibiotic protection against aminopterin in the rat), a 4th series, in which a known protectant (Chloresium, a brand of water soluble chlorophyllin) at a certain dosage level (0.5 milligrams/rat/day) was compared to the same level of SGE. The results of this series with pertinent parameters is rendered in Table I. The "unprotected" aminopterin-dosed animals did poorly, as usual; this being reflected in a fifty percent survival at the termination, failure to gain weight after the second week*, oligocythemia and anemia (the low color index in all groups including the controls is due to inherent iron deficiency of the milk-bread diet), dearth of platelets and granulocytes in the peripheral blood films and a visibly hypoplastic vertebral marrow.

In the group fed chlorophyllin in addition to aminopterin all animals survived; protection was not complete in this instance for, though the weight matched that of the control group, the terminal blood picture was not quite as good. The degree of protection was, however, at least comparable to that procured in earlier conducted series with this material (13). The group re-

*In fact, weight gain during the second week is spurious in this group because aminopterin frequently causes anasarca. There is some degree of the latter even in partially "protected" rats and this may account for the apparent "roughness" of growth curve exhibited in these series.

TABLE I
COMPARATIVE REVERSALS OF AMINOPTERIN TOXICITY EFFECTED BY
STREPTOMYCES GRISEUS FRACTION AND SODIUM CUPRICHLOPHYLLIN

Series	Initial Weight	1st Week*	2nd Week**	3rd Week	Hemoglobin*** Range	Average	RBC Average
1. Control	50.2	61.0	70.2	79.4	85-92	87.4	6.1m
2. Aminopterin	49.8	59.6	68.0(4)	67.1(3)	48-64	56.6	3.4
3. Aminopterin + Chlorophyll	48.4	60.6	66.2	80.8	70-81	77.0	4.6
4. Aminopterin + SGE	50.0	65.5	80.0	88.8	68-96	82.2	7.7
5. Aminopterin + SGE + chlorophyll	49.2	60.2	66.6	81.8	77-94	81.2	5.9****

*Average aminopterin intake 8 gammas per day to this time.

**Average aminopterin intake 12 gammas per day.

***In decimillimels/liter.

(3) Survivors out of an initial group of 6 animals.

****The fact that chlorophyllin detracts from the protection afforded by Streptomyces Griseus Eluate, as evidenced by the parameters in this Group, will not be discussed in the body of this report. Such results however are not out of line with those emerging from poultry feeding experiments in which "APF" substances, while frequently summing their effects, not infrequently do the reverse. Explanations for "neutralizations" of this type, while now necessitated by notorious failure to reduplicate growth promotion experiments with the same APF at different experimental stations, are not here cogent.

ceiving SGE showed a weight gain rate and a hematologic status exceeding that of the controls; a culmination in this type of experiment requiring detailed discussion because they were actually polycythemic. This is not apparent from the hemoglobin determination since that parameter is again limited in this instance by iron availability. However the SGE-receiving rats showed evidence in their peripheral blood smears of augmented hemopoietic marrow activity; this in the face of profound hematomyelotoxic action of aminopterin.*

DISCUSSION

Apparently SGE contains a factor or factors with such marked hemopoietic activity that it not only neutralizes, but actually reverses the action of a cytotoxic agent which has come to be regarded as the most powerful hemopoietic marrow depressant known. No presently defined factor is capable of reproducing SGE's activity unless it be that present in anterior pituitary preparations lately designated as EPH (erythropoietic hormone) or erythropoietin. The presence of such a hormone in crude anterior pituitary extracts was first postulated by Evans in 1933 (14) and Van Dyke and his coworkers have recently adduced considerable evidence for its existence (15). Since this report makes the titular assumption that the hemopoietic factor present in SGE is similar to EPH, one would logically expect us to compare the present material with a known preparation of the pituitary-derived "hormone" in the same connection before ascribing the similarity.**

This is impractical because all available pituitary EPH preparations have not only defined ACTH content but are really crude somatotrophic hormone (STH) fractions. At the same time it must be admitted that SGE has detectable quantities of ACTH by the Sayer's (16) assay procedure and that the vigorous growth of the rats in Group 4 is reminiscent of STH activity. We feel that practical interests are best served at this time by outlining the basis for presence of an EPH-like substance in SGE which requires no more tenuous reasoning than Evans' ascription of EPH to crude anterior pituitary (14). These practical considerations arise around the widespread use of streptomyces-derived supplements in animal and human nutrition and the pressing problem posed by the myelaplastic hematologic dyscrasias which are definitely on the increase and with which we are still powerless to cope. It is believed that any modality

*It may be asked at this point why we do not adduce bone marrow evidence of such hemopoietic overactivity. The avoidance is purposeful at this time because of our own controversial contention that the normal rat's bone marrow is "hyperplastic" by human standards and that the end-product of erythroid maturation in the rat is erythroblast, rather than normoblast-derived.

**Actually it has been found in our own experiments that a preparation of pituitary somatotropin (STH) made available to us by other investigators has conferred comparable protection to aminopterin-poisoned rats under our defined experimental conditions, but we are deferring to these other investigators their own right of priority in designating to their STH preparation a definite EPH content. Adductions of present, indirect evidence for the EPH-like activity of SGE will be from the available literature.

which is a true hemopoietic stimulant, such as the aminopterin-reversing fraction of SGE, or pituitary-derived EPH merits complete discussion.

Van Dyke has shown that pituitary EPH is orally effective (15) and this appears to be the case for SGE which might now tentatively be designated as "streptomyces griseus erythropoietin." To encounter an EPH-like material in a fermentation product is no more remarkable than the presence of an ACTH-like material in the same product (7). That source for the latter material, as well as its presence in enteric commensal organisms (7, 8) has led to the interesting speculation that certain mammals (normally coprophagizing animals such as the rat; animals that depend on rumen fermentations such as the cow) need an enterogenous precursor for pituitary ACTH production (9). This speculation proved profitable for it indicated that ACTH must be absorbable from the bowel which was contrary to all teachings. It necessitated the trial of oral ACTH in experimental animals with the result that it was found to be so absorbed (17). But the original speculation leading to this result had arisen on the basis of otherwise inexplicable clinical observations around adrenocorticomimetic effects of bowel flora modification that were well founded in experience. There may be similar clinical grounding for elucidating the physiologic origin and role of erythropoietin.

Beside the indirect evidence afforded by Van Dyke et al (15) (these workers showed that the anemia of hypophysectomized animals was not duplicated by removal of all endocrine target organs activated by the anterior pituitary) there is clinical evidence for a pituitary EPH. For example, the diabetic child is not only taller, heavier and sexually precocious; coefficients which, like his diabetes are indicative of anterior hypophyseal hyperfunction, but usually has a higher than average erythrocyte and granulocyte count as well. In diabetic coma, where anterior pituitary elaboration reaches its acme, we have frequently encountered erythrocyte counts above eight million and platelet counts of one million. These, along with the marked granulocytosis of diabetic coma are usually ascribed to "dehydration hemoconcentration" but it is fairly obvious that this figure would necessitate loss of half the body water, which is incompatible with life. We have also found this pancythemia to persist during vigorous rehydration therapy. That it is really due to profound hemopoietic stimulation is proved by our finding that the blood cholinesterase level during diabetic coma is extremely high; the blood cholinesterase concentration is now used as an index of hemopoietic marrow activity (18).

It was previously demonstrated that, in conditions with anterior hypophyseal overactivity in humans, the blood cholinesterase level was elevated (19). Because of the porphyrin lacrymation exhibited by unprotected aminopterin-poisoned animals and because cholinesterase injection had been shown to prevent cholinergic porphyrin lacrymation in the rat (20, 21), the parenteral enzyme was administered to such animals in a limited series and seemed to afford protection to the systemic effects of aminopterin (13). This same cholinesterase preparation had been shown to reverse megaloblastic anemia in humans (22). The ad-

ministration of crude *s. griseus* residue has caused polycythemia in patients in which this incursion is not the usual course of the disease (5) and raises the blood cholinesterase in patients in whom the level of that enzyme is inordinately low (25).

From the foregoing, there is an intimate, if still unclarified interrelationship among three factors; (1) fermentation products with hemopoietic effect, (2) an anterior pituitary elaborate with a similar effect, and (3) an enzyme in some way connected, either determinantly or reflectively, with hemopoiesis; cholinesterase. Intensifying this relationship, though still not clarifying it is the recent demonstration that *Ps. Fluorescens*, the intestinal commensal which Takeda et al (8) found to elaborate a corticotropin, is also an adaptive producer of cholinesterase in culture (23). The intimacy of these associations among (1), (2) and (3) shows that there must be a relationship, though one probably as complex as to defy deductive resolution on the basis of presented experimental data. However, some approximation of solution is desirable in view of the present applications of (1) crude streptomyces residues, (2) crude pituitary extracts and (3) cholinesterases in therapeutics. Perhaps we may be guided by this last discipline and assume a solution to our problem on the basis of clinical experience. We can state this solution and see how it accords with presently known fact.

The postulated solution to the problem of the interrelationships sets up a series of premises and shows the connection between each member of the series; (a) a precursor, or prosthesis of pituitary erythropoietin normally arises through microbial activity in the bowel; (b) this prosthesis is absorbed into the portal circulation and must therefore exist, in transit, in the liver. It could likewise be present, also as a transport product, in the bowel mucosa. (c) Upon reaching the anterior pituitary, the prosthesis is stored, modified or elaborated in response to the requirements of the organism. (d) The release of pituitary EPH directly stimulates the hemopoietic marrow to elaborate its peripheropetal elements, granulocytes, erythro-

cytes and thrombocytes* as well as its own humeral contribution, (e) Cholinesterase, ChE. Hemopoiesis homeostasis then becomes contingent on the functional balance between EPH and ChE. To evaluate this hypothesis, one first looks for parallels in other target organs activated by the anterior pituitary and finds such parallels readily constructable. For example, an ACTH precursor is found in microbial fermentations (7) and certain enteric organisms (7, 8) and this precursor is found effective on oral administration. The 11-oxysteroids which its administration calls forth, in turn limits further pituitary ACTH elaboration. Pituitary gonadotropin not only causes spermatocyte maturation with production of spermatozoa, but an accompanying enzyme (hyaluronidase) production as well. We thus find that no extreme novelty attends the hypothesis on the EPH metabolism.

The second examination of the hypothesis, which was adduced from clinical experience, is in the light of how it fits the clinical and experimental facts. The criteria for EPH activity are based on polycythemia production and reversal of aminopterin toxicity. An EPH-like substance has been seen to arise from streptomyces fermentation; it is necessary to demonstrate similar production (a) by bowel organisms. This has not been done experimentally as yet but it may suffice to point out that no known nutritional factor predicated to arise from bowel organisms (B_{12} , the folic acid series, the constituents of the vitamin B complex) are absent from streptomyces residues.

We should expect to encounter an EPH-like substance in (b) either intestinal mucosa or liver, or both. A preparation of the former did protect against aminopterin toxicity in the rat (13) while transient polycythemia have been produced in humans and rats with crude liver extracts, though not with B_{12} . It is possible that EPH will be demonstrated in those B_{12} non-containing mammalian liver extracts lately shown by Williams to protect against radiation morbidity (24). Similar protection is conferred by streptomyces residues (25), as well as by SGE (Table II).

*To do so, EPH would necessarily be a "maturation factor" for the myeloid, erythroid and megalokaryocytic series.

TABLE II
EFFECT OF STREPTOMYCES-DERIVED ERYTHROPOIETIN ON
RADIATION ANEMIA*

Date	Week of Radiation Period	Medication	RBC $\times 10^6$	Hemoglobin dmm/l	WBC $\times 10^3$	Back Pain
11/14/52	0	none	3.41	62	7.8	severe
12/3	3	none	3.29	59	5.3	severe
2/7/53	12	iron- B_{12} -folie	3.10	52	5.7	persistent
3/3	16	iron- B_{12} discon. SGE 0.5 gms started	3.27	50	5.1	persistent
3/12	17		3.63	60	8.4	moderate
4/11	21	SGE contin.	4.33	81	10.6	minimal
4/30	24	SGE contin.	4.52	88	9.7	absent

*Female, age 48, vertebral metastases from breast adenocarcinoma; radiation to vertebral region.

The evidence for a pituitary EPH elaboration mechanism (c) has already been cited and, in this connection it may be remarked that clinicians anticipated this eventuality long before laboratorians demonstrated it. However, this anticipation arose from other than clinical speculations. The anterior pituitary is developed in cyclostomes which do not have a defined adrenal cortex. It arises as an outpouching of the alimentary tract, lending credence to the idea that (like the thyroid of similar genesis), its humeral secretion would be orally effective. Oral pituitary preparations have been long in clinical use but, as stated above, the idea that ACTH is orally ineffective, and that oral administration can thereby separate effects of ACTH from that of presumed EPH is no longer tenable (17). Nelsen et al (7) confirmed that fish meal which has had long utility as "APF" poultry feed supplements contains a corticotropin. Menge et al (26) found that the chick growth factor in fish solubles does, like ACTH, resist acid autoclaving but, unlike ACTH it also withstands alkali autoclaving. Again, unfortunately it is presently impossible to separate this effect from that of STH, as the latter is inseparable from EPH except on the basis of the demonstration of Van Dyke et al (15) that their STH preparation would not prevent hypophysectomy anemia. Contrariwise, Sacchetti and Bianchini (27) describe an STH preparation which, in their hands accelerated hemopoiesis. However, in view of the possibility that this STH contained EPH, the former experiment indicating the negative case must take authoritative preference.

The humeral role of the cholinesterase, ChE, present in a non-nervous tissue such as blood, and the function of this (e), "transport ChE" which, in the human is predominantly erythrocytic and thrombocytic, has only lately had clarification. Substitutive rises in this transport ChE have been attained (28) by the administration of the purified human plasma enzyme* in a variety of clinical conditions (29, 30). However, germane to the present discussion is the fact that the least equivocal results from such administration were forthcoming when Barnard and Fox (30) administered the enzyme to a series of patients with atopic dermatoses. In such cases, the preadministration level of the enzyme is ordinarily *higher* than normal (19). These therapeutic effects were so illogical and confusing that they were presented with the explanation of utter inadequacy of the authors' theory around ChE activity. The presently outlined theory now furnishes a reasonable explanation for these results. If ChE is the target-organ hormone of EPH activity, then EPH elaboration would be governed by circulating ChE level. A further augmentation of an elevated transport ChE would depress that phase of anterior pituitary hyperactivity which may have been responsible for the atopic reactivity in the first place. This mechanism of a target-organ's hormone to depress the cognate "master-hormone" is seen when insulin administration depresses the output of pituitary diabetogenic hormone. Clinically, an excellent example to offer in comparison is that of the undoubted utility of testosterone in Cushing's syndrome, where

*Generously supplied as Choline (human plasma cholinesterase) by Drs. E. B. McLean and F. F. Johnson of Cutter Laboratories, Berkeley, Cal.

it is administered in spite of an already high circulating androgen level and where, nevertheless it proves to be the most efficacious measure available.

Admittedly the picture is a complex one and while an interrelationship scheme among microbially derived precursors, adeno-hypophyseal EPH and transport ChE may be drawn, confusing details must be incorporated. For example, Mian (31) found an ACTH preparation to raise plasma ChE *in vitro*. Davis claimed a similar *in vitro* effect for liver extract or folic acid (32). These effects would eliminate the hemopoietic marrow from the presented interrelationship were it not for the fact that the main fraction of transport ChE in the human, is not that of the plasma (said to be a liver elaborate) but that of the erythrocytes and thrombocytes*.

Further confusion is lent by apparent ability of either ACTH or STH to stimulate erythropoiesis in hypophysectomized rats (27). This may be dispelled when purer extracts are available since ACTH, STH and EPH now available undoubtedly contain traces of each other.

For the positive case, the presented scheme affords a better explanation for more apparently unrelated observations than any heretofore. For example the accelerated growth of non-ruminants, fed antibiotics, surpasses the optimum growth of those reared under sterile conditions. The contribution of intestinal flora to this acceleration is more than passive. The unidentified "vitamins" and "growth factors" arising from the antibiotic-modified flora, to which nutritionists ascribe the growth acceleration could easily be in the category of STH and EPH precursors.

An adaptation mechanism which circumvents the adrenal cortex has long been surmised by physiologists who, though admitting the importance of the pituitary adrenal axis, deny its complete ubiquity in stress reactions. After all, the Addisonian patient or the adrenalectomized animal *does* make some adjustment to stress. Langley has repeatedly demonstrated that the

*We have regarded the plasma ChE as originating from intestinal mucosa because this tissue, like hemopoietic marrow is unusually susceptible to either aminopterin or x-irradiation. Such a source for plasma ChE was suggested by presence of an enzyme with identical characteristics in mucosa and liver; by the drop simultaneously in the intestinal mucosa and blood plasma in irradiated animals (33, 34, 35) and the radiation drop on plasma ChE in humans (36).

After preparation of this report, the prior study of Everett and Sawyer (40) was called to our attention. These investigators (1946) had speculated on the intestinal mucosal source of plasma ChE, with liver storage. However partial hepatectomy, while sharply curtailing plasma ChE concentration, had no effect on that of the remaining liver tissue. They demonstrated that the rise of plasma ChE produced by estrogen administration did not occur when the steroid was given intramenterically and concluded that the production of plasma ChE was mediated by the anterior pituitary. They also cite a case report of high plasma ChE in a patient with adeno-hypophyseal tumor in which no further rise could be produced by estrogen administration. Thus they reported the hypophyseally induced ChE elevation three years before this was reported by the writer's group. While some exception might be taken to the validity of their experimental evidence that the liver, rather than the intestinal mucosa is the site of plasma ChE production, this concept of its concentration regulation accords with our own, to which we add that both plasma ChE and erythrocyte ChE are under direct pituitary humoral control.

adrenalectomized animal responds to anoxia by hemopoiesis (37). The hypophysectomized animal does not (16).^{*} A similar dichotomy between adrenocortical and non-cortical mediated adaptation reactions is unavoidable when one studies the basis for stress decompensations in human patients. Many have, unquestionably, either hypofunction or dysfunction of the adrenal cortex. But others, with apparently adequate adrenocortical mechanisms nevertheless exhibit a type of stress decompensation along with a failure of ChE homeostasis and believed to be contingent on the latter (38). Undoubtedly there is a third category of adaptation failure in which both deficiencies are involved; we believe this to be the case in the malignant hematologic dyscrasias. An even more obvious example may be those inoperable neoplastic diseases where hypoadrenocorticism is frequent (39) (as evidenced by salutary effects of small doses of cortisone or adrenal cortex extract) and where the blood ChE is significantly lowered. It is curious in this connection that, along with reports on the benefits to be derived from hypophysectomy in some patients with advanced cancer, we are receiving parallel reports from abroad on the utility of crude anteropituitary extracts in the same type of case.

SUMMARY

From a crude streptomyces griseus "animal protein factor" feed supplement in which a corticotropin had been found, an acid eluate of charcoal adsorbate was prepared. In 2 milligram oral daily doses this eluate not only reversed the myeloplastic and cholinergic effects of aminopterin poisoning in weanling rats, but evoked accelerated growth and hemopoiesis in the face of aminopterin administration. It is concluded that the original fermentation broth contained an erythropoietin and a somatotropin in addition to the corticotropin.

Since intestinal commensal organisms including those classified among the enterobacteriaceae have been shown to be a source of corticotropin, it is postulated that microbial sources, including the intestinal flora can engender somatotropic and erythropoietic factors similar to those, or precursors to those produced by the adeno-hypophysis. It is further postulated that pituitary erythropoietin precursor arises from the intestinal flora, is a transient constituent of intestinal mucosa and liver and reaches the anterior pituitary where it is modified to its final elaborate; erythropoietic hormone, EPH.

From the known physiology of EPH it becomes pos-

^{*}In their recent report showing the necessity of the pituitary for the hemopoietic response to anoxia (and thereby adducing additional proof for the existence of the pituitary EPF, which, on injection permitted newborn, hypophysectomized rats to make this response) the Berkeley workers (16) again cite the theory that intrauterine anoxia is the reason for the high fetal erythrocyte count. At birth, with adequate oxygenation, the count drops. This infers that the fetus elaborates EPH. Some work to be published, using the aminopterin-poisoned rat as a test object indicates that the source of this particular EPH may be the placental tissue. Inadequacy of pituitary function immediately after birth could be due, by the present theory, to a lack of an established intestinal flora for some days after birth. It takes over one week for an adequate flora for vitamin K synthesis to materialize and the same interval may be necessary for adeno-hypophyseal humoral precursors.

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sible to assign it a role as the regulator of transport cholinesterase (ChE) metabolism. This conclusion finds gratifying agreement with the demonstrated presence of this enzyme in at least one intestinal commensal organism (*Ps. fluorescens*), in intestinal mucosa, liver and in the presumed target organ of EPH, the hemopoietic marrow.

A complete theory around the interrelationships of EPH and ChE is presented to explain the manner in which erythropoietin or cholinesterase administration may curtail certain cholinergic phenomena seen during aminopterin administration. The theory is examined in light of certain cholinergic manifestations exhibited by patients with depleted transport ChE. In agreement with a previous theory put forward by Everett and Sawyer, it is concluded that the pituitary regulation of ChE level is a component of the stress-compensatory (or "adaptation") syndrome which is not directly contingent on adrenocortical mediation.

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NEOPLASMS OF THE SMALL BOWEL

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THE INCIDENCE of small bowel tumors based on a review of case reports is misleading. Emmett and Dreyfuss (5) found over three hundred cases of malignant small bowel tumors reported in the literature, but felt many successfully treated cases had gone unreported because of their sporadic occurrence. Only those reports which deal with a review of autopsy and surgical pathological material, accumulated over a period of years, will reflect accurately the true incidence of these tumors. On the basis of such data (2, 3, 10, 14, 15) it has been estimated that from 3 to 6% of carcinomas of the intestinal tract occur in the small bowel if carcinoma of the ampulla of Vater is included. Sarcomas of the intestinal tract (6, 7, 11, 16) occur less frequently than carcinoma, but when present, 60% of them are in the small bowel. Benign tumors, possibly because they are more apt to go unrecognized, are reported as being extremely rare (14, 17). Concerning the age incidence, carcinomas are more frequent in the fifth and sixth decades; sarcomas in the third and fourth. Males show about a two-to-one incidence over females.

The classification of small bowel tumors includes the benign forms of adenoma, fibroma, lipoma, myoma, and endothelial tumors and their malignant counterparts of carcinoma and sarcoma. Carcinoma usually occurs in one of three forms:

1. The scirrhotic or annular constricting variety.
2. The polypoid forms, which tend to ulcerate and bleed.
3. The diffuse type, either ulcerating or non-ulcerating.

The scirrhotic form tends to be of lower grade malignancy than the bulkier forms (9). The carcinoid tumors, when they occur in the small bowel, occur most frequently in the ileum. Metastases are found either at autopsy or surgery in 20% of cases of carcinoid of the small bowel (4).

The lymphosarcomas, originating from lymphoid tissue, naturally occur most commonly in the ileum (7). The other sarcomas have about equal incidence throughout the small bowel. A small percentage may appear as multiple lesions, or may appear in the intestinal tract as part of a generalized disease, such as von Recklinghausen's or polyposis. Grossly the growth characteristics of sarcomas are of two types: One is the bulky, soft friable tumor, resembling lymphoid tissue; the other is the firm, hard localized type which, in the less malignant forms, tends to appear encapsulated. They may extend intraluminally or extraluminally, and frequently ulcerate. When primary in the small intestine, a sarcoma may show a tendency to remain localized for a long period of time, which,

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of course, influences the prognosis greatly in contrast to carcinoma. An analogy might be drawn here between sarcoma and carcinoma of the breast.

Frank, Miller and Bell (6), in reviewing 102 cases of sarcoma of the small intestine, classified them as follows:

Lymphosarcoma	66)	
Reticulum cell	3)	69
Leiomyosarcoma	22)	
Myosarcoma	1)	23
Fibrosarcoma	6)	
Neurofibrosarcoma	3)	
Spindle cell	1)	10
Total		102

The symptomatology of a small bowel tumor is obviously dependent on its histology, its location and the particular growth pattern which it follows. In the duodenum, tumors involving the first part nearly always cause acute obstructive symptoms similar to carcinoma of the pylorus. In the second portion of the duodenum jaundice is the most characteristic finding, and in the third portion obstruction, again, is usually produced with the vomiting characteristically containing bile and pancreatic enzymes. The early and insidious development of symptoms of postprandial fullness and discomfort may be the only subjective complaint associated with high partial intestinal obstruction. Cramp-like abdominal pain and distention are usually lacking. Relief may be obtained by vomiting or by simply not eating. The following case report is an example of such symptomatology due to a jejunal tumor:

No. 1 C. S. . . . A 30-year-old white male swimming instructor was first seen in December, 1952, complaining of progressive upper abdominal fullness of two months duration. This was most frequently noticed about four hours after eating his evening meal and was occasionally relieved by vomiting. There was increasing anorexia, but he felt well as long as he didn't eat. He was able to go as long as two days eating only liquids before feeling hungry. Physical examination revealed a well developed, well nourished, white male weighing 201 lbs., whose weight prior to the present illness had been 210 lbs. The only positive physical finding was a non-tender liver palpable two fingers below the right costal margin. No abdominal mass was palpable.

An upper GI series on 12-19-52 revealed a chronic obstruction at the duodeno-jejunal junction, with dilatation of the duodenum. There was a 24 hr. residual of barium in the stomach. A definite lesion could not be demonstrated, and the possibility of superior mesenteric artery compression of the duodenum or regional enteritis was entertained.

An exploratory laparotomy was done on 1-7-53, and

a tumor of the bowel was found near the ligament of Treitz showing invasion of the retroperitoneal fat surrounding a branch of the left colic artery. A bowel resection, including the retroperitoneal fat and vessels was carried out with end-to-end anastomosis. The pathology report was reticulum cell sarcoma. Lymph nodes were not seen or palpated, but a full course of deep x-ray to the mesenteric root was given prophylactically, commencing two weeks postoperatively. The patient is alive and well 18 months later.

Since symptoms may exist for several months before complete obstruction takes place, it is easy to understand how they might at first be considered as "nervous indigestion," food dyscrasia, duodenal ulcer or biliary dyspepsia, and treated symptomatically for a long period before the patient becomes seriously disabled and a more careful search is made for the true nature of the illness. Weight loss is nearly always present, due to gradually increasing anorexia.

Lower down in the intestinal tract the symptoms of intermittent obstruction, due to recurring intussusception, are more common. Sudden attacks of colicky pain may occur, followed in a few minutes or a few hours by complete recovery. Weeks or months may pass before another attack takes place, although the intervals gradually shorten as the attacks become more severe. Since these symptoms frequently respond to the administration of antispasmodic drugs, they may again be attributed to gastroenteritis or "nervous indigestion." If a scar is present on the abdomen, adhesions may be blamed. If only partial lower small bowel obstruction is produced, symptoms such as vague abdominal discomfort, a full feeling, anorexia, and a change in bowel habits manifested by less frequent bowel movements or constipation may be the only complaint.

Bleeding of various degrees of severity is present in nearly all small bowel tumors (2, 6, 9, 13). If the hemorrhage is relatively small but chronic, a mild anemia will be produced with asthenia or fatigability as the only symptom. On the other hand, massive bleeding may be the first indication of disease. The following two case reports presented melena of different degrees as the first symptom.

No. 2. C. F. . . . A 26-year-old white male salesman entered the hospital on 11-2-52 complaining of sudden onset of massive rectal bleeding. There was an associated, mild, subjective discomfort of increased bowel activity and mild tenesmus. There was no history of significant previous gastrointestinal disorder. Physical examination revealed a well developed, well nourished, somewhat pale, white male. Temp. 98.6; pulse 80; blood pressure 120/65. Rectal examination revealed blood clots in the ampulla. Moderate borborygmi were present. Otherwise the examination was negative.

There were 3.71 million RBC's, 10.7 gm. of Hgb., 35% hematocrit, and 12,800 WBC's with a normal differential.

A diagnosis of bleeding peptic ulcer was made and conservative treatment started. However, because of persistent bleeding, surgical consultation was requested. A transfusion was started. A Levin tube was

passed, and aspiration revealed milk curds tinged with bile. Bleeding, clotting and prothrombin times were normal. Upper gastrointestinal barium meal studies were done and failed to reveal any evidence of ulcer. Sigmoidoscopic examination was done and revealed only dark blood coating the rectal mucosa. The possibility of a bleeding Meckel's diverticulum or small bowel tumor was considered, and an exploratory laparotomy was carried out on 11-3-52. An encapsulated tumor 2 cm. in diameter was found situated on the mesenteric side of the mid-ileum. A segmental resection was performed with end-to-end anastomosis. Grossly, the tumor showed a small area of ulceration in the mucosa and on cross-section contained sinuses filled with blood. Microscopically, the tumor was diagnosed a sarcoma of smooth muscle origin probably of low grade malignancy. The postoperative course was uneventful, and patient is alive and well to date.

No. 3. M. V. . . . A 37-year-old county agent was admitted to the hospital on 2-16-53 complaining of black, tarry stools first occurring in November, 1952, and lasting four days. He had been hospitalized at another hospital at that time, given a blood transfusion and dismissed after complete gastrointestinal x-ray series failed to reveal any pathology. He remained asymptomatic for about four months (until 10 days prior to this admission), when he again developed tarry stools which lasted 6 days. Three days prior to admission he again developed tarry stools with associated weakness, dizziness and dyspnea on exertion. Other gastrointestinal symptoms were emphatically denied. There was a history of hypertension, for which he had been taking hexamethonium, and occasional migraine headaches with associated vomiting of greenish liquid. There had been a 20 lb. weight loss in 2 years. Physical examination revealed a well developed, well nourished, pale white male with a B.P. of 140/100 and a pulse of 88. A mass palpated in the RLQ on admission could not be palpated the following day after a bowel movement. Rectal examination revealed the ampulla to be filled with greenish gray fecal matter. Procto-sigmoidoscopic examination was negative.

The hematocrit was 25%; Hgb. 95 gms.; 3.65 million RBC's and 13,100 WBC's with a normal differential. Gastric analysis was normal. Bleeding, clotting times and platelet count were normal. Liver function studies were normal. Complete gastrointestinal x-ray studies showed no pathology.

Four pints of blood were given, and the stools were examined daily for occult blood, since gross bleeding had stopped. On 3-3-53, occult blood was 4 plus, and the next day the stools became grossly bloody again. The diagnosis of a bleeding small bowel lesion, probably tumor, was made, and exploratory laparotomy was performed on 3-6-53. A well encapsulated tumor measuring 9 x 5 cms. was found on the antimesenteric border of the ileum about four feet proximal to the cecum. Segmental resection with end-to-end anastomosis was performed. Grossly, the tumor was soft in consistency, grayish-white in color, and contained many blood filled sinuses. There was a small area of mucosal ulceration. The microscopic diagnosis was neurofibroma. The postoperative course was uneventful, and the patient is alive and well to date.

Rarely, perforation (1) and even massive metastases (13) may be the first manifestation of small bowel tumor, and in such cases the diagnosis is usually made at the autopsy table.

The signs of small bowel tumors usually correspond to the complication produced. A movable abdominal mass may be present in a small percentage of cases (9) and, of course, would aid greatly in making the diagnosis. Usually, however, only the subtle signs of weight loss, intermittent episodes of borborygmi, anemia and mild abdominal distention are found.

The diagnosis of small bowel tumors must begin first and foremost with a suspicion of the presence of such a tumor. Because of their rarity, this suspicion generally results from the exclusion of the more common etiological entities by careful work-up. A history suggesting a more common gastrointestinal disease, but which does not follow the so-called "textbook pattern" should arouse suspicion. A persistent secondary anemia with gross or microscopic melena not explained by other gastrointestinal pathology should likewise arouse suspicion. Finally, any intermittent episodes of abdominal discomfort manifested by characteristic obstructive symptoms, especially when occult blood can be persistently found in the stools, should suggest the possibility of small bowel tumor.

Too frequently complete reliance is made on the x-ray for the final answer; and if negative, the patient is erroneously informed of the absence of pathology, even though the unmistakable symptoms of partial intestinal obstruction and occult blood in the stools may have been present. The confirmation of small bowel tumor by barium meal study is made in no more than 25% of cases (12), and the majority of these are of tumors found in the more fixed portions of the small bowel. By using more careful x-ray techniques (8, 17), including rapid barium meal studies, and by the injection of thin barium through a Miller-Abbott tube at various levels in the small bowel, a greater incidence of x-ray diagnosis of small bowel lesions may be obtained. In general, however, the use of x-ray in the diagnosis of suspected small bowel tumors is most valuable in excluding more common diseases.

Only by exploratory laparotomy or by autopsy can the exact diagnosis be made and, even then, an extremely careful exploration is always necessary. Careful palpation and, more important, visual exploration to the extent that it is technically possible at the time of laparotomy, even in the presence of other pathology, will reveal the presence of a small bowel tumor (3). The last case is an excellent example of such a coincidental finding.

No. 4. M.F. . . . This 57-year-old white male was admitted to the hospital in August, 1953, with a history of four attacks of RUQ pain, chills, fever and nausea of four months duration. There was a 15 lb. weight loss associated with the present illness. Physical examination at the time of admission was essentially negative, except for a palpable liver edge and slight tenderness to the right of the umbilicus. Laboratory studies were all within normal limits except for a non-visualizing gallbladder. Stool studies for occult blood were negative.

Cholecystectomy was performed on 8-31-53. During MARCH, 1955

routine exploration of the abdomen a plaque-like thickening about 1.5 cms. in diameter was palpated and then visualized in the terminal ileum about six inches from the cecum. It was thought to be a fibroma and was locally excised, including a margin of about 1 cm. of normal bowel, and the defect was closed transversely. An appendectomy was also performed. The pathological diagnosis of the tumor of the ileum was carcinoid. Recovery was uneventful.

The treatment of small bowel tumors is resection and end-to-end anastomosis, even if only palliative (5, 12), to eliminate recurring obstruction and hemorrhage. The extent of resection and the amount of mesentery to be included in the resection depends on the type of tumor, the presence or absence of lymph node involvement and the location of the tumor. The variability of these factors leaves the final decision as to the extensiveness of resection up to the judgment and skill of the operator. X-ray therapy in cases of lymphosarcoma of the small bowel, when the tumor is not resectable or when lymph node metastases extend beyond the limits of resectability, have resulted in remarkable results. Faulkner and Dockerty (7) report its use in 82% of their postoperative patients who have lymphosarcoma of the small bowel, with two cases of 5-year survival using irradiation alone. Gunkler (10) reports a reticulum cell sarcoma of jejunum surviving 8 years with deep x-ray therapy following surgical bypass of the tumor.

The prognosis of tumors of the small bowel, as reported in the literature, has been poor primarily because of the greater incidence of carcinoma and the presence of metastases in twenty-five percent of cases at the time of surgery (13, 15).

Sarcomas, on the other hand, have a much better prognosis for cure because they tend to remain localized, are usually slow to metastasize and are more radiosensitive. Earlier diagnosis and treatment would, of course, greatly improve the prognosis with any of these tumors, since hardly any other intraabdominal tumor lends itself so readily to resection and, therefore, to what should be a high rate of curability.

SUMMARY

Tumors of the small bowel are uncommon and comprise about 5% of all gastrointestinal tumors. Carcinoma exceeds sarcoma in frequency, although of the sarcomas which occur in the gastrointestinal tract, 60% are found in the small bowel. Benign tumors of the small intestine are reported as extremely rare because they are more frequently asymptomatic. The early symptomatology is usually that of partial or intermittent intestinal obstruction although complications such as hemorrhage, perforation or complete obstruction may be the first to occur. The correct diagnosis is infrequently made, but should be seriously considered when the characteristic syndrome of a more common disease is bizarre, or whenever barium studies fail to reveal the suspected pathology in cases with anemia and melena. The treatment of small bowel lesions is resection and end-to-end anastomosis, which, except for the fixed portions of the small intestine, is technically simple and should be attended by a low incidence of morbidity and mortality. Al-

though carcinomas tend to metastasize earlier than sarcomas, the usual constricting nature of their growth should result in earlier diagnosis and treatment, with a better prognosis than has been reported in the past. This can only be accomplished by constantly keeping the possibility of small bowel tumor in mind. One should never be satisfied with negative gastrointestinal studies once the ominous symptoms and findings of partial intestinal obstruction or melena have been observed.

Four cases of small bowel tumor are described and include a reticulum cell sarcoma of jejunum, a leiomyosarcoma of mid-ileum, a neurofibroma of lower ileum and a carcinoid of the terminal ileum.

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ABSTRACTS ON NUTRITION

DEWHURST, K.: *A case of scurvy simulating a gastric neoplasm.* Brit. Med. J., Nov. 13, 1954, 1148.

The case of a man of 70 is described. He presented a bizarre combination of findings—bright blood in the stools, fits of epilepsy, subcutaneous petechiae, and mental lethargy. He had been living alone and subsisting on a meager diet of bread and milk and some various soups. There had been a marked weight loss of 28 pounds. Hematemesis had occurred on several occasions. X-ray films of the barium-filled stomach suggested a cancer in the pre-pyloric area. However, biopsy taken through a gastroscope very close to the lesion showed normal mucosa with hemorrhage. On intensive treatment with ascorbic acid he rapidly improved. The epilepsy was controlled with phenobarbital. Repeated x-ray examination of the stomach revealed that the lesion had disappeared, and it was assumed to have been a gastric hematoma.

HUBBLE, D.: *Insulin resistance.* Brit. Med. J., Oct. 30, 1954, 1022.

A unique instance of insulin resistance is reported in a diabetic girl. The maximum daily dose of insulin used was 19,250 units. The resistance was phasic. When menstruation was established the resistant phases were usually premenstrual and the sensitive phases post-menstrual. Urinary endocrine surveys showed no remarkable deviations from average findings. It is assumed that the growth hormone had a hand in this

case of insulin resistance. The patient, tall at the onset of diabetes, grew very rapidly taller but only during phases of resistance. The correct treatment of insulin resistance, says Hubble, is to overcome it by using insulin in adequate doses.

RAICHAUDHURI, B. AND GHOSH, S. C.: *The study of the nature of intravenous glucose tolerance test in marasmic babies.* Calcutta Med. J., 51, 3, March 1954, 87.

Intravenous glucose tolerance tests in marasmic babies showed initial slight hypoglycemia and slight elevation of blood sugar curves at the end of one hour. However, it was obvious that the mechanism of maintenance and utilization of blood glucose in marasmic babies is not much upset even in the late stages of the morbid process.

FORSHAW, J. W. B.: *Idiopathic hypochromic anemia in males.* Brit. Med. J., Oct. 16, 1954, 908.

Eleven cases of hypochromic anemia in males is added to the list, indicating that from 4 to 8 percent of cases of hypochromic anemia occur in males. Of course, the majority occur in women. All cases responded well to iron administration and the majority remained well after treatment. Judging from two quotations from Shakespeare, the playwright was not only well aware of the "green sickness" in men, but traced it to a low-protein diet.

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WADSWORTH, G. R.: *Hemoglobin levels of normal men and women in a tropical climate*. Brit. Med. J., Oct. 16, 1954, 910.

Several physiologists have noted decrease in hemoglobin levels in men living in hot rooms from a few days to a few weeks. The author found, however, that the hemoglobin levels of 337 men and 116 women of different races living in Singapore were at a high normal. The mean concentration for men was 16.12 gms. per 100 ml. and for women 13.88 gm. per ml. Previous observations referred to could only have been a temporary effect.

CROWE, P. J. AND GOULSTON, S.: *Post-gastrectomy dietary management*. Med. J. Australia, Sept. 11, 1954, 430.

(The authors state that evidence has been presented to indicate that pulmonary tuberculosis occurs more commonly after partial gastrectomy than in patients with an intact stomach). The symptoms of the post-gastrectomy syndromes are reviewed. The importance of diet is emphasized. The gastric remnant "requires education" in its handling of foodstuffs. Frequent feedings high in protein are recommended for the first 3 months and specimen dietary regimes are described.

COX, F. J. N. AND PUGH, R. J. P.: *Galactosemia*. Brit. Med. J., Sept. 11, 1954, 613.

Galactosemia is a rare condition in which from birth the child is unable to metabolize galactose, the latter appearing in the urine. Liver enlargement and cataracts are part of the later picture and the disease is fatal, being associated with mental deficiency. With proper diagnosis and treatment life may be saved and a normal child result. Benedict's solution gives a positive reaction and there are further tests for the identification of galactose. The essential measure in treatment is the exclusion of lactose and galactose from the diet and the use of a lactose-free milk.

COBLEY, J. F. C. C., HARRISON, K. S., BLACKET, R. B. AND HEWITT, L. E.: *Out-patient assessment of the "novo" insulins*. Med. J. Australia, Sept. 25, 1954, 499.

Trials of "Lente" insulin have been made in the out-patient department of the Royal Prince Alfred Hospital for 7 or 8 months. Using urinalysis as the chief method of control it was found that most patients did better on Lente insulin than on either soluble or Z. P. insulin, but there were some cases who did not do so well. It is possible that in-patient studies with blood

sugar curves will help in deciding the real advantages of the one-injection-daily method.

POMERANZE, J., BEINFELD, W. H. AND CHESSIN, M.: *Serum lipid and fat tolerance studies in normal, obese and atherosclerotic subjects*. Circulation, 10, 5, Nov. 1954, 742.

Fat tolerance tests demonstrated elevated and prolonged post-prandial lipemia in markedly obese, hypercholesteremic and atherosclerotic subjects when compared with normal individuals. An improvement of this abnormal fat tolerance was achieved following rigid fat restriction in hypercholesteremic and atherosclerotic persons and following weight reduction in the extremely obese. An inferential relationship is suggested between extreme obesity and atherosclerosis.

WICKES, I. G.: *Fetal defects following insulin coma therapy in early pregnancy*. Brit. Med. J., Oct. 3, 1954, 1029.

The case is described of a mentally defective child with hypertelorism and optic atrophy who was born to a schizophrenic woman who had received insulin coma therapy from the second month of pregnancy. Probably the insulin, or the anoxia induced by it, was responsible for the fetal defects. A study of the small number of previously reported cases suggests that insulin may be injurious only when given before the tenth week.

GIRDWOOD, R. H.: *Rapid estimation of the serum vitamin B₁₂ by a microbiological method*. Brit. Med. J., Oct. 23, 1954, 954.

The serum level of vitamin B₁₂ was estimated by a *Lactobacillus leichmannii* growth method in 36 patients with pernicious anemia in relapse, 24 patients with other forms of megaloblastic anemia, 55 persons who did not suffer from megaloblastic anemia, and 20 patients with pernicious anemia under treatment. The level was less than 130 micro-micro-grams per ml. in 34 out of 36 cases of pernicious anemia in relapse, in one patient who had megaloblastic anemia and another with macrocytic anemia after partial gastrectomy, in one with idiopathic steatorrhea, and 3 other persons, two of whom had macrocytic anemia with normoblastic marrow and who responded to vitamin B₁₂ therapy. It exceeded 130 micro-micro-grams per ml. in all the other patients tested.

The method is speedy, and together with the differential urinary-folic-acid-excretion test is of value in the investigation of complex cases of megaloblastic anemia.

EDITORIAL

THE SPLENIC FLEXURE SYNDROME

It has become apparent to those internists who have looked for it, that a long splenic loop of the colon may, on its own account, produce symptoms which are unusually disturbing inasmuch as they closely resemble those of angina pectoris. Patients showing this "splenic loop syndrome" usually have normal cardiograms and also hearts which, from the roentgen and clinical aspects, do not give evidence of disease. Again, we may find cardiographic evidence of myocardial impairment, in which case we may assume that the pressure of the filled splenic loop against the diaphragm is merely an abetting cause of heart pain.

The pain or distress described by these patients usually is located subternally or, at times, precordially, and reference of the pain to the left arm is very common. As a rule there is no definite relationship of the pain to exertion and usually constipation of varying severity is present. Furthermore, the pain may

not be of short duration, as in ordinary angina, but may persist for hours at a time.

The therapeutic test is very important in making a diagnosis of splenic loop syndrome. An enema of any kind which quickly empties the left colon brings prompt relief. Other subsidiary points in treatment are low-roughage diet, sedative and atropine in sufficient doses to bring about relaxation of the colonic musculature. The use of mineral oil, or similar products, usually assists the patient in avoiding painful episodes.

To the list of common conditions causing anginal pain, such as gallbladder disease, peptic ulcer and diaphragmatic hernia, we must now add the splenic loop syndrome. In all these instances we feel that true heart pain is present, but improvement or cure of the pain is possible by treatment directed toward the abetting cause. In some cases of splenic loop syndrome, a resection of the loop seems to be a clearly desirable measure.

BOOK REVIEWS

TEXTBOOK OF THE ROENTGENOLOGICAL DIFFERENTIAL DIAGNOSIS. DISEASES OF THE ABDOMINAL ORGANS. (VOL. 2). (LEHRBUCH DER ROENTGENOLOGISCHEN DIFFERENTIALDIAGNOSTIK. BAND 2. ERKRANKUNGEN DER BAUCH ORGANE). Werner Teschendorf, Koeln. 1037 pgs. 1610 illustrations. George Thieme, Stuttgart, 1954. Third enlarged and improved edition. \$44.30.

We want to congratulate Teschendorf on the third edition of his book on roentgenology, for it is an outstanding work. Just to mention one fact, whereas the first edition contained some 900 illustrations, the third edition contains over 1600 illustrations of the highest quality. Thieme has produced a book which will be one of the basic works in the roentgenology of the abdomen. The clearness of reproduction and text can hardly be surpassed. We have only praise for Teschendorf's book, which is known to many. The entire armamentarium of roentgenology is used for demonstrating pathological processes. There are many pages and innumerable illustrations on mucosal studies. Spot films of all parts of the alimentary tract are used. The quality of the illustrations is on such an even level that it seems that all the films were taken during the last year. The new advances of gallbladder and intravenous cholangiography are discussed as Teschendorf is among the first in pioneering in this new road in roentgenology. T. is no stranger to Americans where some of his latest studies in this field have been published on the pages of this journal. The text, too, has been supplemented since the second edition by several hundred pages. The book is written in German, but the illustrations are so perfect, that it can be easily

used as an atlas, even if one is not fully acquainted with the language. Besides, the gastrointestinal tract, the liver, spleen and kidneys are discussed.

Among the very important parts of the book, is a section on the operated stomach. This field has not been well presented in other publications, therefore, it will be appreciated by everyone. Many films show the misleading interpretation of films, for instance, due to artifacts, and the correct interpretation is given. A section on small intestinal pathology is especially exhaustive. The index of the book is very complete, comprising 57 pages. The literature concerning every topic is at the bottom of every page.

We would like to recommend T's. book to all those interested in roentgenology, gastro-enterology, surgery and internal medicine. There is an extensive bibliography at the bottom of every page, which covers the American literature to a large extent. Our congratulations to Teschendorf and Thieme publishing house. Franz J. Lust.

MINUTES OF THE GERMAN SOCIETY FOR DIGESTIVE AND METABOLIC DISEASES 1953. (VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FUER VERDAUUNGS- UND STOFFWECHSEL KRANKHEITEN, XVII. TAGUNG). Dr. H. W. Bansi, Editor. 340 pages, 152 illustrations, 51 tables. Georg Thieme Verlag, Stuttgart 1954. \$11.45.

At this meeting of the well known society, four main topics were discussed. The first one dealt with iron metabolism and liver. Masshoff, Heilmeyer, Kalk, Stich, Remy and Lange were the speakers. Haemochromatosis in its different aspects was presented. The

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second topic dealt with colitis ulcerosa. The speakers were: Henning, Baumgaertel, Deucher and Petzold. The latter discussed bacteriotherapy in unspecific colitis. The third topic was: Thyroidea and iodine, which was presented by Bansi, Jores, Horst, Fellingner, Strauss and Hiller, Kuhlencordt, Kracht, Jacob, Klein, Remy, Gerlich, Lang and Heinsen. The very important subject of cholangitis was discussed by: Selberg, Markoff, Lodenkaempfer, Mallet-Guy, Eicholz, Lauda, Kald, Wildhirt, Gorss, Kirnberger, Maring, Stimming, Witte, Franke, Loeweneck, Goetze, Boller, Willert, and Roettger. The discussions were at their usual high level. We can recommend the book to all those interested in gastroenterology and bacteriology and metabolic diseases. The articles are written in German, the illustrations are very good.

Franz J. Lust.

DIAGNOSTIC ADVANCES IN GASTROINTESTINAL ROENTGENOLOGY. Dr. Arthur J. Bendick. 131 pages, 75 illustrations. Grune and Stratton, New York, 1954. \$6.00.

Dr. A. J. Bendick is well known for his work on the

roentgenological examination of the gastrointestinal tract. In 1948 he introduced the use of club soda to demonstrate pathology of the stomach and duodenum. His new book is written from personal experience, which he gained from many years of practice and as director of the roentgenological department of the Beth Israel Hospital in New York City.

Bendick gives a clear description of his technique, which is very thorough and enables the demonstration of the smallest pathological changes in the stomach and duodenum. All those who are not familiar with his work have to adjust themselves to read films taken after administration of club soda. He uses spot films extensively, which were thought to be harmful about twenty years ago. Examples of his films illustrate this well written book. We read it from cover to cover and have learned a great deal. The illustrations are very good, the index exhaustive. We can highly recommend the work to all those interested in gastroenterology and roentgenology, which means that the book will be read by many surgeons. We congratulate Bendick on his outstanding book!

Franz J. Lust.

GENERAL ABSTRACTS OF CURRENT LITERATURE

GATES, G. E.: *Incidence of intestinal side-effects with tetracycline*. Jour. Indiana Med. Assn., Oct. 1954, 1101.

In the treatment of 100 patients with Achromycin® in private practice the incidence of intestinal side-effects was decidedly low. One case developed definite diarrhea and six others noted temporary slight looseness of the stools in a frequency of only 1 to 3 stools per day. Few patients reported slight nausea, and another had slight anal pruritus of short duration. No other ill effects of the drug were noted. The broad spectrum effects of the drug were fully substantiated.

SAAVE, J. J.: *Appendicitis in the tropics, and its pitfalls: a clinical investigation with report of two cases*. Brit. Med. J., Sept. 18, 1954, 465.

The author describes in detail two cases of appendicitis in New Guinea natives. Appendicitis is rare among primitive peoples, or at least it is seldom recognized and treated. Saave lists eleven different diseases which may resemble appendicitis among the natives of New Guinea. These are mostly infestations, as well as Weil's disease, relapsing fevers, enteric fevers, spider poisoning, bubonic plague, and lymphogranuloma venereum.

BOLLINGER, J. A.: *Mortality factors in acute small bowel obstruction*. U. S. Armed Forces Med. J., 5, 10, Oct. 1954, 1448-1455.

Of all types of small bowel obstruction, mesenteric thrombosis carries the highest strangulation rate and consequently has the highest mortality. There seems to be a gradually increasing incidence of small bowel obstruction. During the period 1945-1953 in St. Francis Hospital, Evanston, Illinois and the U. S.

Air Force Hospital, Bolling Air Force Base, Washington, D. C., there has been a decline in the surgical mortality in the more recent years. In the earlier portion of the period studied, the mortality rate was 14 percent, which had decreased to 6.6 percent at the end of the study. The increased incidence of small bowel obstruction is the result of greater frequency of surgical exploration and the increasing longevity of the present-day patient. Mortality may be reduced by earlier diagnosis of strangulation obstruction, recognition of closed loop obstruction, limiting unsuccessful decompression therapy to 24 hours, use of wide spectrum antibiotics and judicious use of fluid and electrolyte supply.

HARDAWAY, R. M. III: *Gastric resection in military personnel*. U. S. Armed Forces Med. J., 5, IV, Oct. 1954, 1467-1468.

Hardaway notes that if seven-eighths of the stomach is removed for peptic ulcer, there is great likelihood of an unfavorable post-operative course, consisting of colic, dumping syndrome, hypoglycemia, loss of weight and inability to carry on militarily. Consequently he removes only two-thirds of the stomach. This gives good results and permits the patients to perform a maximum of effective military duty.

McKIRDIE, M.: *Early diagnosis of the acute abdomen*. Northwest Med., 53, 9, Sept. 1954, 897.

In 200 consecutive laparotomies performed for severe abdominal pain, a wrong diagnosis was made in 17 percent. The majority of the mistakes were made in small bowel obstruction. In 50 percent of those who died, death was preventable. In another series of 124 cases, there was a diagnostic error of 26.6 percent. McKirdie makes a plea for better "work-ups" and more clear thinking.

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NYHES, R. E. AND BURKE, E. C.: *Pseudomembranous enterocolitis: medical treatment with recovery*. Proc. Staff Meet. Mayo Clin., Sept. 1, 1954, 513.

A boy of nine with bronchitis, who received aureomycin, 125 mg. four times daily for 16 days, developed a pseudomembranous enterocolitis associated with an intestinal infection by staphylococci. He recovered as a result of supportive treatment, and the use of erythromycin and hydrocortisone.

LOVSHIN, L. L.: *Headache and peptic ulcer*. Cleveland Clin. Quart., 21, 4, Oct. 1954, 230.

Seven patients with peptic ulcer who were subjected to vagotomies and in whom excellent results were obtained as measured by disappearance of gastrointestinal symptoms and healing of ulcers, were later seen with chief complaint of headache. The headaches could be classified as being due to sustained muscle contractions of the head and neck in 5 cases and extracranial vascular in 2 cases. The basic disease in these patients is neither peptic ulcer nor headache—it is a defect in total life adjustment.

ALTHAUSEN, T. L. AND UYEYAMA, K.: *A new test of pancreatic function based on starch tolerance*. Ann. Int. Med., 41, 3, Sept. 1954, 563.

The basis of this new test is that pure starch is less completely converted to glucose in persons with pancreatic disease. Using a specially prepared starch meal, a "starch tolerance test" is done by estimating blood glucose before and at intervals following the meal. Also, a glucose tolerance test must be done for comparison. In normal persons, the blood sugar curves obtained by the two tolerance tests are almost identical, whereas, in pancreatic disease, a very flat "starch curve" is obtained. A study of the tests and the controls indicates that this new test probably will prove of great value in estimating pancreatic function.

SHEHADI, W. H.: *Oral cholangiography with telepaque*. Am. J. Roentgen., Rad. Ther. and Nuc. Med., 72, 5, Sept. 1954, 436.

Shehadi has found telepaque to be the most valuable medium for x-ray examination of the gallbladder, but especially valuable because the bile ducts may frequently be visualized 10 minutes and 40 minutes following the fat meal. Many illustrations are presented showing as good visualization of the cystic and common ducts following oral administration of telepaque as was obtained by injection of contrast media during operation. This paper suggests that with care and careful radiographic technique, the bile ducts (except the hepatic radicles) may be satisfactorily visualized after the oral administration of telepaque. Such a procedure, once it has been refined and further studied, will take its place as a very important and simple method of studying the bile ducts at any time, even following cholecystectomy.

SCANLAN, R. L. AND YOUNG, B. R.: *The roentgen diagnosis of gallbladder and biliary tract disease without cholecystography*. Am. J. Roent., Rad. Ther. and Nuc. Med., 72, 4, Oct. 1954, 639.

It is shown that prone, supine and lateral films are of value in assessing a gallbladder, even without the

administration of a cholecystographic medium. This is true particularly when opaque stones are present. When the "spread" of these stone shadows is great or between the various views, it indicates a large gallbladder. Sometimes the outline of a thickened gallbladder can be seen, the inferior margin of which is frequently outlined by contiguous gas-filled loops of bowel.

LICHTENSTEIN, M. E.: *Anatomic dangers in gallbladder surgery*. Illinois Med. J., 106, 4, Oct. 1954, 233.

Location and size of the incision are factors that determine the ease with which surgery on the biliary passages may be accomplished. It is better to do well what needs to be done than to hurry the procedure and risk an accident. Time is not a factor so long as it is not wasted. In short or obese patients, an oblique or transverse incision exposes more of a field than a longitudinal incision. When the patient is tall and has a "long" abdomen, the longitudinal incision is better. Every incision should be "custom tailored" to fit the patient.

BALDREE, C. E., JR.: *Surgical implications of acute pancreatitis*. Illinois Med. J., 106, 4, Oct. 1954, 248.

Surgeons of the St. Louis University Group are practically unanimous in their opinion that operation is not indicated in the treatment of acute pancreatitis itself. Occasionally it may be necessary to operate for spreading peritonitis with the use of simple drainage of the pancreatic area, sometimes with drainage also of the biliary tract. Surgery is reserved for the complications—pseudo-cysts, pancreatic abscess, etc.

FITZSIMMONS, E. L. AND BURNIKEL, R. H.: *Carcinoid tumors of the rectum*. J. Indiana State Med. A., 47, 11, Nov. 1954, 1282.

A case of carcinoid tumor of the rectum is reported. Such tumors are neoplasms of potential malignancy and usually slow growing. All patients with submucosal nodules should be urged to have them removed for biopsy purposes, even though they are asymptomatic.

MARSHAK, R. H., WOLF, B. S. AND ADLERSBERG, D.: *Roentgen studies of the small intestine in sprue*. Am. J. Roentgen., Rad. Ther. and Nuc. Med., 72, 5, Sept. 1954, 380.

The diagnosis of sprue can be made from the symptoms and laboratory investigations, the chief features being steatorrhea, weight loss, anemia, oral lesions, hypocalcemia, hypoproteinemia, flat vit. A and glucose tolerance curves and normal pancreatic enzyme studies. From the standpoint of the x-ray findings in the small intestine, a very few show normal pattern, while the vast majority show dilatation in the mid- and distal jejunum, segmentation, thickening of the mucosal folds and the presence of hypersecretion of an altered quality. A lesser number of patients show a second type of pattern—segmentation is marked, early and persistent and present throughout the small intestine, secretions are pronounced and dilatation is slight to moderate. While such findings may occur

also in nephrosis, hyperthyroidism, cirrhosis, pancreatic steatorrhea, pellagra and other deficiency states, they are more constant and characteristic in sprue. X-ray evidence of improvement in the sprue pattern was significant in 3 patients treated with Cortisone and in 4 who received anti-anemic therapy for many years.

HORLICK, L.: *Serum lipoprotein stability in atherosclerosis*. *Circulation*, 10, 1, July 1954, 30-42.

A lecithinase extracted from cultures of *Cl. Welchii* (alpha toxin) when added to human blood serum produces a turbidity of the serum. It was found that this turbidity developed much more rapidly in persons with atherosclerosis than in normal or young persons. The turbidity formation appears to depend on factors which govern lipoprotein stability. The final degree of turbidity correlates well with the serum lipids as measured quantitatively. This turbidity test certainly serves as a screening technique for detecting individuals with abnormal serum lipid levels and also as a means of separating individuals with coronary sclerosis from a control population.

LEMAK, L. L., WIGBY, P. E. AND MARTIN, J. E.: *Peptic ulcer in children*. *Texas State J. M.*, 50, 11, Nov. 1954, 772.

The authors present 6 cases of peptic ulcer in children aged 7 to 12 years. In this age group the chief symptom is upper abdominal pain, sometimes associated with nausea and vomiting. Some of the cases responded well to medical treatment while others did not respond well. The x-ray examination of children for peptic ulcer is not easy, inasmuch as cooperation for spot films is difficult to obtain. In some of the cases, psychological predisposing causes were obvious. It is not generally realized how frequently children may develop peptic ulcer. In infancy most of the ulcers are gastric, and there is a marked tendency to hemorrhage and/or perforation. In the childhood group the duodenal ulcer is much in preponderance and the symptoms are like those in adults. All children with characteristic ulcer symptoms should be carefully x-rayed.

BISGARD, J. D.: *The cancer-ulcer problem of the stomach*. *Illinois Med. J.*, 106, 5, Nov. 1954, 291.

While there is a minority of cases of gastric cancer which are hopeless from the start, owing to early metastases, it is also true that the majority of cases reach the surgeon several months or even years after the onset of symptoms. These symptoms may be like those of ulcer, and may respond to ulcer regimens. Therefore, when an ulcer of the stomach is found by x-ray, a strict ulcer regimen should be used for 3 weeks, and if relief is not obtained, exploration should be made. In some cases where the ulcer appears to get smaller on such treatment, repeat films should be made every 2 weeks until a definite opinion is obtained.

DANSTROM, J. R., LOWRY, D. C. AND COLVERT, J. R.: *Benign gastric ulcer of the greater curvature*. *Am. J. Roentgen., Rad. Ther. and Nuc. Med.*, 72, 5, Sept. 1954, 426.

Six cases of benign ulcer of the greater curvature of the stomach are presented with films. Although the majority of gastric ulcers of the greater curvature

are malignant, x-ray examination does offer evidence that certain of these ulcers are benign.

SAINT, E. G.: *Acute pancreatitis*. *Med. J. Australia*, Oct. 2, 1954, 536.

Epigastric pain with severe reference to the back is highly characteristic of pancreatitis. When in doubt the serum amylase test is diagnostic. Pancreatitis may be acute and fulminating or chronic recurrent, sometimes with only mild discomfort. In the acute disease, operation is best avoided, and reliance placed on antibiotics, electrolytes, etc., gastric aspiration, etc. Atropine or Banthine are both useful drugs. Saint thinks that pancreatitis in the obese, in diabetics and in middle-aged females may owe its origin to disordered lipid metabolism and/or arteriosclerosis.

BOURGEON, R., PIETRI, H. AND GUNTZ, M.: *The interest of transsplenic splenoportography in the hepatic echinococcosis*. *Archives des Maladies de l'Appareil Digestif et des Maladies de la Nutrition*. T. 43, No. 2, Feb. 1954, pp. 168-176, 7 fig.

To Abeatici's and Campi's technic of the transsplenic splenoportography, the authors have brought the following modifications: the radiological examination is made under a pneumoperitoneum; the films are taken with the incidence of procubitus.

The pneumoperitoneum and the procubitus show in a very good light the outlines of the liver and of the spleen—and the drawing of the splenoportographies is no longer isolated but replaced in its actual anatomic frame.

Applied to the echinococcosis of the liver this method gives information of the same kind as that supplied by the cholangiography: identification of the deep hydatid cysts, otherwise inaccessible to physical exploration; diagnosis of unicity or multiplicity of the echinococcal damage of the liver; diagnosis of the functional or atrophic areas of the parasited liver—and a recognition of the areas of compensating hypertrophy.

Guy Albot.

PIETRI, H. AND MASSONNAT, J. (ALGIERS): *The Interest of the pneumoperitoneum in the radiologic study of the cirrhotic liver*. *Arch. Mal. App. Dig.* T. 43, No. 2, Feb. 1954, p. 159-167.

After a brief period of favour about the year 1920 (thesis of Coliez and Lacayo) the radiology of the liver under pneumoperitoneum has fallen into the most undeserved oblivion.

In France we are indebted to Porcher for the rehabilitation of the pneumoperitoneum as a means of diagnosis; this author has well shown in his study of the upper pole of the stomach, all the interest of this means of contrast, its simplicity and its usual innocuousness.

Thus our essay appears under more favorable auspices. The radiology of the cirrhotic livers under pneumoperitoneum is a part of a combination of investigations, such as the detection of oesophageal varices or splenoportographies.

The technical problem offers no difficulties; under pneumoperitoneum there exists but one position

which always gives the silhouette of the liver and of the spleen, and this position is the abdominal decubitus.

The other incidences (upright—lateral decubitus—dorsal decubitus) badly isolate the hepato-splenic outlines.

The quantity of air to insufflate is two liters—for the ascitic patients.

The ascites when it exists, must be entirely emptied.

The study of the films gives remarkable indications as to the hepatic and splenic morphology: the least alterations of the hepatic surface stand out and the embossments of the nailed liver appear as actually pathognomonic ones.

Besides, the reading of the films brings a pretty accurate volumetric notion of the liver and spleen. The importance of the atrophy, the density of the "nailed pictures" are sometimes such that a mere glance is enough to estimate the potential of the hepatic gland, in other words is enough to formulate a prognostic opinion.

A splenoportograph supplements these data and informs us about the portal system on the image of blockage and of shunts. These give a survey of the hepato-splenic group of its splenoportal duct, which somewhat represents a panoramic view of the cirrhosis.

The radiology of the liver under the pneumoperitoneum seems to be about to gain a superior place in the series of functional and prognostic explorations of cirrhotic syndrome.

Guy Albot.

DUNN, R. M. AND CONOMY, A. B.: *Carcinoma of the body and tail of the pancreas: a study based on twenty cases.* Med. J. Australia, Aug. 21, 1954, 277.

The almost hopeless prognosis of cancer of the body and tail of the pancreas is emphasized, the average length of life after first symptoms being nine months. Diagnosis is impossible without exploratory laparotomy which should be done as early as possible, especially in males between 40 and 60 who complain of epigastric pain referred to the back and in whom clinical and x-ray examinations are negative. Seventeen of their twenty cases were explored surgically. In the only one in which cancer of the body and tail was suspected, no carcinoma was found, but rather a peptic ulcer penetrating the pancreas with a large mass in the lesser sac. From the standpoint of prognosis, this lesion is probably the worst of all intra-abdominal neoplasms, and this state of affairs can only be remedied by learning more about etiology and early diagnosis.

KATZ, I. AND ARCOMANO, J.: *Roentgen findings in a case of perforation of the cecum by a bone.* Radiology, 63, 3, Sept. 1954, 411.

A case of perforation of the cecum in which a bone producing the perforation was visible on plain roentgenograms is presented. The patient was operated on because of an abdominal mass, and the presence of the bone was revealed by x-ray examination of the opera-

tive specimen. Subsequent review of the pre-operative films showed the bone as a linear shadow in the right lower quadrant. This illustrates the possibility of a correct preoperative diagnosis in such instances.

RAY, H. N. AND GUPTA, P. C.: *A cytochemical study of entameba histolytica.* J. Indian Med. Assn., 23, 12, Sept. 1954, 529.

The authors present the results of cytochemical studies of trophic and cystic forms of *E. histolytica* for the presence of mitochondria, Golgi complex, nucleic acids, phosphatases, glycogen and lipids. Mitochondria were found in the endoplasm of the trophic forms and they showed oxidation-reduction phenomena. The Golgi complex is present in the endoplasm and is spheroidal in structure. The ameba is rich in ribonucleic acid (R.N.A.) and contains relatively minute amounts of deoxyribonucleic acid (DNA) in the nucleus. The chromatoid bars are made up mainly of RNA and DNA and contain the phosphatases. There is evidence of active DNA-RNA turnover taking place in these structures. Alkaline phosphatase is present in the nuclear membrane and the karyosome and less frequently in the nucleoplasm and in the outer border of the ectoplasm, at times exhibiting a bilaminar pattern. Acid phosphatase is present in the nucleus along the nuclear membrane and often the nucleoplasm; endoplasm also shows a weaker reaction. The cysts show positive reaction for this enzyme both in the nucleus and the endoplasm. The chromatoid bars show marked reaction for phosphatase. Glycogen is present in the endoplasm of the trophic and cystic forms. Minute particles of lipids are distributed throughout the endoplasm of the trophic form.

PALMER, E. D.: *Clinical problems at the esophago-gastric junction.* Am. Pract. & Dig. Treat., 5, 10, Oct. 1954, 764.

Classical concepts of the cardia deserve questioning because "dead anatomy" has been too freely translated into living anatomy. It is well to view disease of the distal esophagus and the cardia in terms of gastric as well as of esophageal anatomy. Palmer shows instances where the gastric mucosa intrudes from 4 to 5 mm. above the cardia, or further. Some hiatus hernias can only be demonstrated by x-ray with abdominal pressure.

HAYES, D. W.: *The irritable bowel syndrome.* Am. Pract. & Dig. Treat., 5, 10, Oct. 1954, 787.

Among the points of interest which Hayes emphasizes are that useless surgical operations for spastic colon are as common now as a decade ago and that the most effective form of treatment is a change of environment. Hayes thinks that resting before eating is of value. Simple psychotherapy is nearly always needed. Hayes does not over-emphasize the advantages of the low-residue diet, but regards such a diet as valuable at the beginning of treatment. Sedatives and antispasmodics help, but are not curative.

HOERR, S. O.: *Cancer of the stomach.* Cleveland Clinic Quart., 21, 4, Oct., 1954, 205.

A clinical classification of gastric carcinoma based on the presence or absence of metastases and the degree

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of invasion by the primary tumor help us to understand the disease by clarifying the curability at the time of operation. A laparotomy is needed to find out the clinical stage of the disease, and a tissue diagnosis is always desirable to bring to light tumors that might be radiosensitive. Clinical estimates are subject to grave errors. About one in every 5 resections is a total gastrectomy. In 21 cases of scirrhous carcinoma, there were no cures.

HUGHES, E. S. R. AND KERNUTT, R. H.: *Operative cholangiography*. Brit. Med. J., Sept. 11, 1954, 620.

The injection of contrast media into the common bile duct via an ureteric catheter followed by x-ray films, with the abdomen open, but before radical surgery, is of definite value in helping to determine the cause of obstructive jaundice. Stones sometimes are thus demonstrated. The procedure, however, has proved disappointing as a routine method. It is valuable in cases with current symptoms following cholecystectomy.

WOOLLEY, E. J. S.: *Pathological changes in the liver in Salmonella typhi-murium infection*. Brit. Med. J., Sept. 11, 1954, 623.

Although the liver changes associated with Salmonella infections seldom are mentioned, Woolley presents a case which shows that hepatic cirrhosis may result. The microorganism was resistant to all antibiotics including chloromycetin.

MCLENNAN, I. AND WATT, J. K.: *Justification for appendectomy in chronic appendicitis*. Brit. Med. J., Sept. 25, 1954, 736.

While there is much dispute as to the existence of chronic appendicitis, the authors regarded it as present when the patient had recurring attacks of subacute pain in the right iliac fossa or at the center of the abdomen. A large number of such cases had their appendices removed and in a very high percentage of those operated upon, no recurrence of the pain was noted after a number of years. The degree of inflammation or its absence, as determined by histological examination, bore no relationship to the improvement or its lack. In men, duodenal ulcer can mimic this so-called chronic appendicitis.

HUGHES, E. S. R.: *Cecostomy*. Med. J. Australia, Oct. 16, 1954, 617.

In cases of acute obstruction due to cancer of the colon or rectum, Hughes prefers a cecostomy to a colostomy opening for relief. One great advantage is that cecostomy leaves the transverse colon quite free to be mobilized in the event of an extensive resection of the colon. Furthermore, a "tube" cecostomy closes spontaneously when the tube is removed.

PARKER, R. G. F. AND KENDALL, E. J. C.: *The liver in ulcerative colitis*. Brit. Med. J., Oct. 30, 1954, 1030.

Post-mortem studies of the livers in 73 cases of ulcerative colitis showed a remarkable dearth of significant changes. Some fatty changes were present in 9 of the 39 cases examined microscopically. Cirrhosis was

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present in only one case, with biliary obstruction. There appears to be little if any increased liability to the development of cirrhosis in these patients as compared with the population as a whole.

SCHRADE, W. AND HEINECKE, R.: *The Postprandial Collapse-Reaction in Patients with Gastric Resection*. Medizinische. 2, 3. Jan. 1954.

That part of the Dumping Syndrome which occurs in many patients with gastric resection immediately after eating is not the result of an abnormal fall of blood sugar but it is due to a reaction of the circulatory system. The alimentary-produced change in the circulation in patients with gastric resection was studied after giving 100 gms. of Dextrose. Systolic and diastolic blood pressure, pulse, elastic and peripheral resistance, stroke volume, minute volume and cardiac capacity (using the method of Wezler-Boeger) were measured. Characteristic effects were observed which followed an abnormal hyperemia of the splanchnic bed during the absorption of the easily digested substances. Syncope occurred in some patients. One can produce the same circulatory changes in unoperated normals by a intrajejunal sugar tolerance test. The osmotic effect of the ingested substance is not the main factor in the pathogenesis of the syndrome as is shown by studies with various hypertonic solutions. The syndrome for which the name "Postprandial collapse-reaction" is proposed, can be treated with diet and drugs with specific peripheral circulatory effects. However, the most satisfactory results are produced with a tightly bound abdominal binder which is used by the patient during eating. By eating while lying down the additional orthostatic circulatory load is avoided.

COLP, RALPH AND JEMERIN, E.: *Is total gastrectomy justified in carcinoma of the stomach?* N. Y. State J. Med. 55, 1, 75. Jan. 1, 1955.

Despite an increase in the resectability of carcinoma of the stomach through technical advances and extension of operative limits, the surgical mortality has considerably lessened. Coincidentally there has been an improvement in results as evidenced by a comparison of recent and older three and five year survival rates. The question has been raised as to whether a further improvement in long-term results would not be obtained by the more frequent or routine use of total gastrectomy even in early limited lesions.

While the mortality of total gastrectomy has been much reduced, it remains appreciably higher than that for subtotal resection. It is likely that any increase in survival would be outweighed by the greater death rate from the procedure. Moreover, morbidity and invalidism following total gastrectomy are significant features. Total gastrectomy does not solve the problem of eradicating lymphatic spread beyond the limits of technical accessibility, and this is the condition responsible for most survival failures. A significant improvement in long-term survival will probably depend upon earlier diagnosis when the lesion is still relatively confined, permitting the performance of a standardized radical subtotal gastric resection. Total gastrectomy should be reserved for those cases in which the entire or proximal stomach is involved.

Franz J. Lust

REPORT FROM THE A.M.A.
INTERIM MEETING
SYMPOSIUM ON HYPERTENSION
AND ARTERIOSCLEROSIS

One of the greatest problems of the physician today is keeping abreast with the rapid advances in the medical sciences and the practice of medicine. If you were not present at the American Medical Association Interim Meeting, at Miami, Florida, December 2, 1954, I am certain you will be interested in a report on the Symposium on Hypertension and Arteriosclerosis presented by a panel of distinguished physicians.

Dr. Victor H. Kugel, Chief of the Department of Cardiovascular Diseases, Mt. Sinai Hospital, Miami Beach, Florida, moderator, opened the session, and in his remarks pointed out that great strides have been made in the therapeutics of hypertension.

Dr. E. Cowles Andrus, Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, the first speaker, stated the objective of all anti-hypertensive therapy—to gradually reduce blood pressure to safe levels. Symptomatic therapy should not be relegated to the past. Sedation, judicious use of the thiocyanates, and weight reduction when necessary, are all of value. Salt restriction below 2 Gm. daily is usually impractical because of poor patient cooperation. Dr. Andrus stated that surgical sympathectomy should be used in critical cases of hypertension where medical therapy has failed.

Dr. J. Gordon Barrow, Associate in Medicine, Emory University School of Medicine, Atlanta, Georgia, discussed the use of the veratrum alkaloids and rauwolfia and its derivatives. The toxic and therapeutic effects of veratrum are encountered in the same range, making effective use of this agent in the routine therapy of hypertension impractical. Veratrum is, however, of value in the management of hypertensive crises, and combination therapy with rauwolfia may have some merit in mild cases.

Rauwolfia and its derivatives are most useful in mild cases of hypertension and as adjunctive therapy to more potent agents in moderate and severe cases. Dr. Barrow stat-

ed that 100 mg. of the whole root, 2 mg. of the alseroxylin fraction and 0.1 mg. of reserpine are equivalent in therapeutic effect. The patient will probably benefit from the sedative and tranquilizing effect of the drug, even if there is no reduction of blood pressure. Side-effects such as nasal stuffiness, diarrhea, unpleasant dreams and nightmares usually disappear as therapy is continued, or upon reduction of dosage. Severe mental depression may occur, requiring discontinuance of therapy.

Dr. J. Edwin Wood, Jr., Professor of Internal Medicine, Department of Medicine, University of Virginia, Charlottesville, Virginia, explained the action of the ganglionic blocking agents, hexamethonium and pentolinium tartrate (ANSOLYSEN*). He reiterated the advantages of Ansolysen over hexamethonium: longer duration of action, predictable oral response, less drug tolerance and fewer by-effects from parasympathetic blockade. For these obvious reasons, he has discontinued the oral use of hexamethonium. He stated that he is attaining excellent results with Ansolysen.

Dr. Wood discussed the technic of therapy with Ansolysen, pointing out the need for individualizing the dose to the needs of the patient. Therapy should be initiated with small doses, gradually increasing until the effective maintenance level is reached.** It was emphasized that normal bowel function must be maintained when this effective agent is used. It is better to prevent constipation than to treat it.

Dr. George E. Burch, Professor and Chairman of the Department of Medicine, Tulane University, School of Medicine, New Orleans, La., discussed hydralazine and the use of drug combinations in the management of hypertension.

The acute and more formidable chronic toxic effects of hydralazine preclude the use of this agent. Speaking throughout of only one combination, rauwolfia and Ansolysen, Dr. Burch emphasized that with proper technic, patients respond well, and, more important, can lead relatively normal and useful lives. Therapy is initiated with rauwolfia and if blood pressure is not adequately reduced, Ansolysen is added to the regimen. Diet is liberal, eliminating only known salty foods such as peanuts, an-

chovies, potato chips. This takes advantage of the potentiating effect of moderate salt intake on Ansolysen and allows for smaller doses. The occurrence of postural hypotension signifies effectiveness and should not be feared. Slight reduction in dose is all that is needed.

Dr. Burch concurred with Dr. Wood in the value of home blood pressure recordings, but advises that a member of the family, not the patient, should take the readings. The physician should instruct the patient about the by-effects from parasympathetic blockade. If the patient understands the action of the drug and knows that he can counteract the by-effects by promptly treating them, he will give better cooperation.

Marked advances have been made in the treatment of hypertension in the past few years. The outlook for the patient with hypertension was never more bright.

*Trademark.

**The continued regulation of dosage should be made according to home recordings of standing systolic blood pressure when practical.

ROBITUSSIN®

In treating cough in childhood, Drs. Kenneth Blanchard and Ralph A. Ford of East Orange and Belleville, N. J., found Robitussin (Robins) "to be a very effective preparation." It also "seemed to follow the criteria laid down by Fantus" with relation to taste and eye appeal. Robitussin's principal ingredient is glyceryl guaiacolate, which by stimulating the production of respiratory tract fluid helps remove the cause of the cough instead of smothering it temporarily. It also contains desoxyephedrine, which tends to maintain the smooth muscle of the respiratory tract in a state of normal tone.

The investigators describe their study of 76 infants and children, "with various types of respiratory infection," of whom 36 were hospital patients and 40 were ambulatory. The study is published in *Journal-Lancet* (74:443 (Nov.) 1954).

Twenty-one of the hospital patients had pertussis, but had not received pertussis immunization. None of the 36 refused to take Robitussin. "Most of the children liked the taste, and no disagreeable side effects such as nausea, vomiting, or loss of appetite were observed," the authors report.

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In comparing the results in the use of Robitussin in the treatment of whooping cough with previous methods of treatment, they state that "the severity and number of cough spasms have been reduced at least 50 per cent, and the duration definitely shortened." The efficacy of Robitussin "can be attributed to its expectorant, demulcent, and general antitussive qualities resulting from an increased respiratory tract fluid. No previous medication was of any real value in treating pertussis."

Of the ambulant cases, they said, "mothers reported excellent results in six to eight days, and on further examinations in the office, the lack of rales and cough verified their reports."

DR. GRAHAM M. CHEN, ONE OF FEW CHINA-BORN SCIENTISTS IN U. S., IS MAN OF MANY ACCOMPLISHMENTS AND FACETS

Detroit.—One of the few China-born scientists in America, Dr. Graham M. Chen, is directing an intensive search here for new drugs to control or cure diseases that attack the human nervous system.

His official title is laboratory director in pharmacodynamic research for Parke, Davis & Company, which—in layman language—means that he heads a team of experts who are studying the nature and properties of drugs, particularly their actions.

But he is a man of many more accomplishments and facets. For example, he holds four degrees: B.S. in science, M.A. in science, Ph.D. in electrochemistry, and M.D. He is one of the few people in the United States who can play ancient, intricate Chinese musical instruments. He grows nearly 200 different varieties of roses in his backyard. And he has four brilliant children, including a daughter at Wellesley and a son at the University of Michigan.

BROTHER IS WITH CHIANG KAI-SHEK ON FORMOSA

Dr. Chen was born Oct. 21, 1903, in the village of Kinwha, about 300 miles south of Shanghai. Kinwha is in the province of Chekiang, which also is the birthplace of Chiang Kai-Shek. Dr. Kuan Chen, a brother of the Parke-Davis scientist, is a physician with Chiang Kai-

Shek's Nationalist forces on Formosa.

Dr. Chen's late father was a lawyer and one of the first Christians in China. He left the country after the Boxer Rebellion and came to Ann Arbor, Mich., where Dr. Chen joined him after getting a B.S. in science from Hanchow Christian College in 1924.

In 1930, Dr. Chen received a Ph.D. in electrochemistry from the University of Michigan, then worked in physiological research for two years at the University of Chicago. In 1932, he returned to China to become instructor in pharmacology at Peiping Union Medical College, where he met his wife, the former Martha Choy, also a teacher. She was born in Honolulu and educated at the University of Michigan. Dr. Chen later became associate professor in pharmacology at Peiping Union Medical College, where he met his wife, the former Martha Choy, also a teacher. She was born in Honolulu and educated at the University of Michigan. Dr. Chen later became associate professor in pharmacology at Peiping Union Medical College.

The Japanese Army came in 1937 and assigned two Japanese medical men to oversee operations at the college, an American school. The United States began repatriating Americans, and Dr. Chen's wife and their first two children were moved to a protected compound. Dr. Chen, not then a U. S. citizen, was prevented from entering.

HAS DONE IMPORTANT WORK ON MAJOR NEW MEDICINALS

A year later, he followed his family back to the United States and became a research fellow at the University of Chicago. Meanwhile, he studied at Rush Medical College, now part of the University of Illinois, and received his M.D. in 1942. He went into war work immediately at the University of Chicago, doing chemical warfare and antimalarial research.

Dr. Chen joined Parke-Davis in 1946 to take charge of a section in general pharmacology. He became laboratory director in pharmacodynamic research in 1952.

He and his associate pharmacologists are seeking new anticonvulsant agents, new antihistamines and new antispasmodics. They are studying the degenerative diseases, hypertension and circulatory disturbances—conditions which have

achieved new importance with the extension of man's average life span. They use highly intricate equipment, including the electroencephalograph, which records drug-induced changes in brain wave patterns.

Major new products on which they have done important work in recent months included Serfin, a pure crystalline alkaloid of Rauwolfia serpentina used in the treatment of hypertension; Ambodryl, an antihistamine which is effective against a wide variety of allergies; and Milontin, an anticonvulsant used in the treatment of petit mal epilepsy.

RELAXES WITH FAMILY, ROSES AND MUSICAL INSTRUMENTS

Dr. Chen finds relaxation with his family, his roses and his ancient Chinese musical instruments. The Pi-pa looks something like a guitar. The Erh-hu is a two-string instrument. The Sheng resembles a miniature pipe organ. There are two flute-like instruments, the Hsiao and the Ti.

But his favorite is the Ching, a seven-string instrument whose history goes back to 1000 B.C.

AGING

A one-day symposium on "Constructive Medicine in Aging: Predictable Stresses in Middle Life" attracted more than 300 physicians to Cincinnati's Netherland Plaza Hotel December 14, to hear papers presented by some of the nation's leading authorities on Gerontology.

Sponsored by The Wm. S. Merrell Company, the scientific session is part of a long range program recently adopted by Merrell in its concentration of research in the field of geriatrics. Last fall Merrell dedicated a new Gerontological Laboratory and its scientists are dedicating themselves to the development of drugs aimed at the chronic diseases of later life. Nelson M. Gampfer, Merrell president and general manager, pointed out as he opened the meeting.

As outlined in advance plans the symposium fulfilled a four-point objective: 1) Seminar exploration of fundamental clinico-research problem of gerontology; 2) Integrate basic research with practical application to clinical medicine; 3) Focus public and professional attention on the growing problem of aging; 4)

Encourage young professional men to select gerontology as a "career."

Speakers who helped develop the program included: Dr. Elmer Hess, Erie, Pennsylvania, president-elect of the American Medical Association; Dr. Edward J. Stieglitz, Consultant in Geriatrics to Veterans Administration, St. Elizabeth's Hospital, Washington, D. C.; Dr. Robert B. Greenblatt, Professor of Endocrinology, Medical College of Georgia, Augusta, Georgia; Dr. Preston A. McLendon, Professor of Pediatrics, George Washington University School of Medicine, Washington, D. C.; Dr. Paul Starr, Professor of Medicine and Chairman of the Department of Medicine, University of Southern California, Pasadena, California; Dr. Wm. D. Stroud, Professor of Cardiology, Graduate School of Medicine, Philadelphia, Pennsylvania; Dr. Lloyd James Thompson, Professor of Psychiatry and Chairman of the Department, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, North Carolina.

Moderators for the session were: Dr. Marion A. Blankenhorn, Director of the Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio; and Dr. Robert C. Rothenberg, President of the Cincinnati Academy of Medicine, Cincinnati, Ohio.

Dr. Rothenberg, commenting on the symposium and the array of distinguished medical men and women in attendance noted that "not too long ago a professional society might have been coy about joining a commercial organization in setting up such a meeting." On the other hand, no Merrell products were mentioned at the meeting and no obvious Merrell identity with the symposium was attempted.

"Anticipatory medicine is applied foresight," Dr. Stieglitz pointed out in his keynote address. "Its application requires the conscientious and mutual concern of the physician and the patient. If it is sensible for a child to prepare to be an adult, so is it sensible for the 'young' person (40) to prepare for age," Dr. Stieglitz said. "Long life in itself is not enough. It is equally important that the later years be lived in health and happiness. For this reason, there is much room for improvement in

therapy aimed at preventing or ameliorating the suffering brought on by the chronic diseases of the aging," Dr. Stieglitz added.

"There is no male Climacteric," Dr. Hess stated flatly. "Men don't go through the change physiologically or psychologically in anything comparable to woman's experience," the AMA's president-elect said.

Dr. Paul Starr told his fellow physicians that the production of thyroid and adrenal hormones in the "normal" old person was not dangerously lower than it is in the younger person. And since these are the hormones which enable an individual to meet stress, it follows that aging men and women have a good chance to meet the problems of old age if they anticipate the invasion of chronic diseases with help from modern therapy.

"Every physician should keep himself reminded of the importance of advising the young couple to meet parenthood with happiness and interest, rather than nervousness and fear; of giving and receiving for themselves and child, 'trust' not just security," said Dr. McLendon as the discussion moved from consideration of age to youth.

"Patients with healed Myocardial Infarction should work," was Dr. Stroud's recommendation. "It is better that the patient fill out his life with rewarding work rather than worried rest," he said.

"Middle age should be counted as somewhere about the 50-year mark," Dr. Thompson suggested in his discussion on "Stresses in Middle Life as Seen from the Psychiatrist's Viewpoint." "Society in general fosters a rather dismal outlook for aging," Dr. Thompson said. He urged that life be looked forward to as a whole, that even from childhood the individual be trained to develop in social-emotional maturity, not expecting sharp transitions, but progressing evenly with acceptance of the difficulties advancing age may entail and also with realization of the richness which years can confer.

The lectures were of sufficient importance that the Academy of General Practice members attending were awarded seven hours formal credit for this symposium.

Reprints and abstracts of papers will be made available later through The Wm. S. Merrell Co.

NEW JERSEY ACADEMY OF MEDICINE HOLDS HEPARIN CONFERENCE

A special Heparin Symposium was held on December 16 by the Academy of Medicine of New Jersey at Newark. Moderator for the symposium was Dr. Irving S. Wright, Professor of Clinical Medicine at Cornell Medical School and Past-President of the American Heart Association. Guest speakers were: Dr. James Barron, Associate Surgeon at the Henry Ford Hospital, Detroit; Dr. John W. Gofman, Associate Professor of Medical Physics at the University of California, Berkeley; Dr. Jere W. Lord, Jr., Professor of Clinical Surgery at New York University; and Dr. William T. Foley, Chief of the Vascular Clinic at New York Hospital. Subjects of the speakers at the symposium were the use of heparin in thromboembolic disturbances arising in the venous system, the clearing factor and subjects related to atherosclerosis, the use of heparin in cardiovascular surgery, and the organization of a heparin team in a hospital. The proceedings of this symposium will be published in the Bulletin of the Academy. A film giving the view of the speakers is being prepared for showing to medical groups throughout the country. Physicians interested in arranging to view the film, should write to the Academy of Medicine of New Jersey, 91 Lincoln Park South, Newark, New Jersey.

AIR FORCE GENERAL SETS MEETING DATE

General Otis O. Benson, Jr., of the U. S. Air Force Medical Service, and currently head of the Aero Medical Association, announced that this organization would hold its 26th Annual meeting at the Hotel Statler, Washington, D. C., from March 20 through 23rd, 1955.

He stated that medical people from many countries throughout the world were expected to attend and participate in the presentation of scientific reports on aviation medicine. In addition to the scientific program a variety of activities have been planned. A dinner has been set at which time there will be a nationally famous speaker and the association will make its annual awards. There will be a business luncheon, exhibits, and an extensive

program for the members of the Wives Wing, the Ladies Auxiliary.

The first meeting of the association was held October 7, 1929, during which it was established that one of the primary aims would be to promote safety in aviation. This aim has been fulfilled over the years until the organization now exercises international influences in stimulating the science and art of aviation medicine.

MILES LABORATORIES BUYS BISCHOFF COMPANY

Walter R. Beardsley, president of Miles Laboratories, Inc. of Elkhart, Ind., has announced that negotiations have been completed for the purchase of the Ernst Bischoff Company of Ivoryton, Conn., manufacturers of biologicals and pharmaceuticals for almost 50 years. The Bischoff Company will henceforth be operated and merged with the Ames Company, subsidiary of Miles Laboratories.

The principal products of Bischoff are My-B-Den, Aminet, Diatussin and several other specialty items for the medical profession. Ames Company now sells Clinitest, Decholin and other diagnostic and pharmaceutical specialties.

Charles F. Miles, president of Ames Company, stated that an expanded sales and development program is being planned for the Bischoff line and that the facilities in Ivoryton will be maintained and enlarged.

DONNATAL®

Donnatal® Extentabs (Donnatal Extended Action Tablets).

Description: Each "Extentab" contains hyoscyamine sulfate 0.3111 mg., atropine sulfate 0.0582 mg., hyoscine hydrobromide 0.0195 mg., and phenobarbital 48.6 mg. ($\frac{3}{4}$ gr.).

Action and Uses: Donnatal Extentabs are so constructed that the equivalent of one Donnatal tablet is released for immediate action and the remaining active ingredients are released gradually and uniformly over a period of 8 to 10 hours to provide sustained therapeutic effects for 10 to 12 hours.

Dosage: Average dose for "round the clock" action: 1 Extentab morning and night.

Available: Pale green, coated tablets in bottles of 100 and 500.

Source: A. H. Robins Co., Inc., Richmond 20, Va.

MARCH, 1955

PHENAPHEN®

Phenaphen® No. 4 (Phenaphen with codeine phosphate 1 gr.).

Description: Each capsule contains acetylsalicylic acid 162.0 mg., phenacetin 194.0 mg., phenobarbital 16.2 mg. ($\frac{1}{4}$ gr.), hyoscyamine sulfate 0.031 mg., and codeine phosphate 64.8 mg. (1 gr.).

Action and Uses: Phenaphen No. 4 provides relief in pain of greater intensity, with minimal possibility of side effects. It frequently makes unnecessary the use of addicting narcotics.

Dosage: As the physician may direct.

Available: Green and white capsules in bottles of 100 and 500.

Source: A. H. Robins Co., Inc., Richmond 20, Va.

NOTICE OF A COURSE IN THE CLINICAL PATHOLOGY AND PATHOLOGY OF PARASITIC DISEASES

A short intensive course on the laboratory diagnosis and pathology of parasitic infections will be presented August 15-27, 1955, at the Louisiana State University School of Medicine in New Orleans.

The course is designed primarily for pathologists and technologists. However, general practitioners, internists, pediatricians, gastroenterologists and physicians engaged in the practice of public health and tropical medicine who are interested in the laboratory diagnosis of parasitic infections are welcome to attend. The instruction and training will be of assistance to pathologists who are preparing for board examinations, to pathologists and physicians who are responsible for the diagnosis of parasitic infections in their laboratories and to technologists engaged in this specialty.

The course will include lectures, extensive demonstrations, films and supervised individual laboratory study. Emphasis will be placed upon the practical aspects of laboratory diagnosis of common parasitic infections, including training in stool examination and stool concentration techniques. Abundant material from patients with parasitic diseases endemic in this area will be available for examination. Comprehensive slide sets containing parasitic organisms in tissue sections will be studied. Library facilities are avail-

able. The medical school building is air conditioned.

Registrants should bring their microscopes, equipped with mechanical stages, and their microscope lamps. A limited number of places will be available. The fee for the course is \$50.00.

Persons interested in attending this course may write to: Dr. Clyde Swartzwelder, Department of Microbiology, Louisiana State University School of Medicine, 1542 Tulane Avenue, New Orleans 12, Louisiana.

CHLOROPHYLLIN FOUND TO INHIBIT HEMAGGLUTINATION CAUSED BY NEWCASTLE DISEASE, MUMPS, INFLUENZA VIRUSES

Memphis, Tenn.—Chlorophyllin has been found to inhibit agglutination of chick red blood cells by the viruses of influenza, mumps and Newcastle disease.

It is generally accepted that agents which thwart this activity of viruses may simultaneously check their infectivity.

Chlorophyllin apparently accomplishes this by a direct effect on the virus as well as by preventing the viruses' occupation of red blood cell receptor sites.

Dr. Wolcott B. Dunham of the General Medical Research Laboratory of the Veterans Administration Medical Teaching Group Hospital here, has reported on his experimental work with chlorophyllin and viruses in a paper published in *Proceedings of the Society for Experimental Biology and Medicine* (87:431, 1954).

In the experiment, solutions of copper chlorophyllin inhibited agglutination or "clumping" of chick red cells when the viruses were used in partially purified suspensions and also when they were precipitated with methanol and washed, Dr. Dunham learned.

All of eleven copper chlorophyllin samples provided by Rystan Company, Mount Vernon, N. Y., inhibited hemagglutination by viruses of the three diseases.

The sample selected by Dr. Dunham for thorough testing showed no undesirable effect on the cells regardless of the concentrations used.

Dr. Dunham emphasizes the increasing order of effectiveness against influenza, mumps and New-

castle disease viruses. This finding is in accordance with an order of activity established for the three viruses; the influenza virus is most active in occupying red cell receptor sites and mumps and Newcastle disease are less active, respectively.

Part of the effect was exerted immediately or within one-half minute of the time the virus and chlorophyllin were mixed with one another. However, the effect increased with increased time of exposure of virus to chlorophyllin. Dr. Dunham suggests, therefore, that the virus itself, as well as the blood

cell, undergoes change. He points out that chlorophyllins have been found to inhibit hemagglutination by a variety of unrelated substances, in addition to these three viruses.

Changes of pH were not found to affect the activity. Nor did dialysis, or separation of crystalloids and colloids, alter chlorophyllin's activity. The active element is evidently not in the dialyzable fraction.

(Chlorophyllins have been found to be suitable for injection and to be free of side effects. Dr. Dunham's work suggests they can modify viral infections. Thus they may

prove useful in prophylaxis or treatment of viral diseases, either as additives for vaccines or as actual viral vaccines when combined with live virus.

The chick red cell system, with which Dr. Dunham's work is concerned, is commonly used for assay of viruses and screening of antivirals. It is also used for the detection of antibodies in the serum of immune subjects. The ability of serum to inhibit hemagglutination is taken as evidence of immunity.)

CCDA-CMRA MEMBERS TOUR PFIZER'S RESEARCH FARM AT VIGO

January 20, Terre Haute, Ind.—Seventy-five members of the Chemical Commercial Development and the Chemical Market Research Associations, on their way to a two-day meeting in Chicago stopped here yesterday to tour the Pfizer Agricultural Research and Development Farm.

The visitors spent the afternoon inspecting the barns, laboratories and other buildings that comprise the 700 acre research center. They heard Dr. Jasper H. Kane, Pfizer vice president, describe the role Pfizer research has played in the advance of animal health as well as human welfare.

Dr. Kane sketching the Farm's place in the general research program carried on by Pfizer, said that the results of experiments and tests at the Terre Haute installation had clearly demonstrated the value to agriculture of such a research unit.

Dr. Herbert G. Luther, director of the Pfizer Farm, and J. J. Thompson, manager of the Agricultural Sales division also addressed the group. Dr. Luther told how research and planning, including nutritional trials of thousands of poultry, hogs and cattle had led to the discovery of Vigofac, a new growth stimulant recently announced by Pfizer scientists.

Special railroad cars took the CMRA-CCDA members from Terre Haute to Chicago where their annual session was to be devoted to discussions of chemistry in foods and feeds.

In his remarks, Dr. Luther also referred to Pfizer's long-time association with the food and beverage industries. The Brooklyn firm makes a variety of vitamins and

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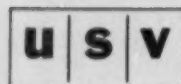
delightfully flavored digestive-nutritive tonic

Each fluid ounce (approx. 2 tablespoonfuls)
provides:
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	pancreatin	126 mg.
	pepsin	126 mg.
lipotropics...	Betaine HCl	100 mg.
	Betaine Monohydrate	200 mg.
	Liver Concentrate*	220 mg.
B complex vitamins...	Yeast Extract*	220 mg.
	Vitamin B ₁₂	4 mcg.
	Inositol	100 mg.
	Thiamine HCl (B ₁)	4 mg.
	Riboflavin (B ₂)	2 mg.
	Pyridoxine HCl (B ₆)	2 mg.
	Panthenol	2 mg.
	Niacinamide	20 mg.
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	Manganese Glycerophosphate	15 mg.

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quickly blocks the nervous
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other chemicals used in the preservation and fortification of food and beverages.

Chas. Pfizer & Co., Inc., Brooklyn, has announced personnel moves in two of its research divisions:

Dr. I. A. Solomons has been appointed Assistant Director of Chemical Research and Development, and Dr. C. I. Jarowski has been named Manager of the Pharmaceutical Research and Development department.

Dr. Solomons, a graduate of the University of Georgia, holds a

Ph.D. in Chemistry from the Polytechnic Institute of Brooklyn. He has been manager of the Brooklyn Chemical Research department since 1952. He joined Pfizer in 1943.

Dr. Jarowski, with Pfizer since 1948, is a graduate of the University of Maryland, School of Pharmacy, and earned his Ph.D. at the same school.

DON'T RUB SNOW ON FROSTBITE

The time-honored custom of rubbing frostbite with snow is outdated,

according to Drs. W. O. Kleitsch and E. K. Connors, Creighton University School of Medicine, in a report in *Postgraduate Medicine* (16: 191 (Sept.) 1954). Today's accepted treatment consists of rapid thawing of the frozen areas by baths somewhat above body temperature, they state.

After thawing takes place, the investigators recommend drying the extremity and spraying it with an aqueous solution of the antibacterial agent, Furacin®, which is described as having a "therapeutic spectrum peculiarly effective in the control of skin organisms." Avoid greasy or oily applications, the authors advise, as they may lead to maceration and infection.

After necrotic tissue is removed and defects are closed by appropriate trimming of the skin flaps, Furacin gauze dressings are applied. The article reports on several cases in which this therapy was employed with excellent results.

INCREASED COMPETITION LIKELY IN PHARMACEUTICAL INDUSTRY DURING 1955, PARKE-DAVIS PRESIDENT SAYS

Harry J. Loynd, president of Parke, Davis & Company, said in a year-end statement today:

"Greatly-intensified competition is likely in the pharmaceutical industry during 1955.

"Growth of the 1,200 or more companies in the industry will depend largely on what may be developed from basic research, combined with sound sales promotion, production and distribution.

"Scientists everywhere are edging closer to the answers to heart attacks, cancer and other degenerative diseases. It is hoped that we will be in a position to offer a commercial polio vaccine sometime during 1955.

"Another factor in the industry's growth will be the expected population increase of over a million people in the United States alone during the coming year. In addition, there will be an expanding emphasis on better health in most countries overseas, which should create many more opportunities.

"Increased competition cannot help but benefit the general public, as well as the industry."

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Tablets 5mg.
homatropine
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for the "squeeze" of g.i. spasm

antispasmodic action
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Each yellow tablet of MESOPIN-PB
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in white tablets, green elixir, and powder.

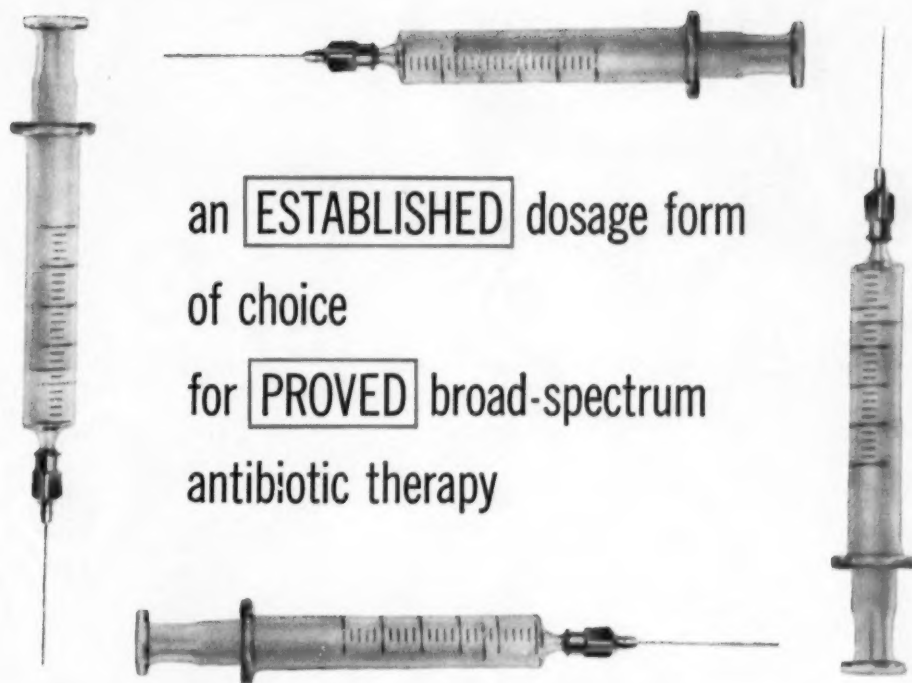
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an **ESTABLISHED** dosage form
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for **PROVED** broad-spectrum
antibiotic therapy

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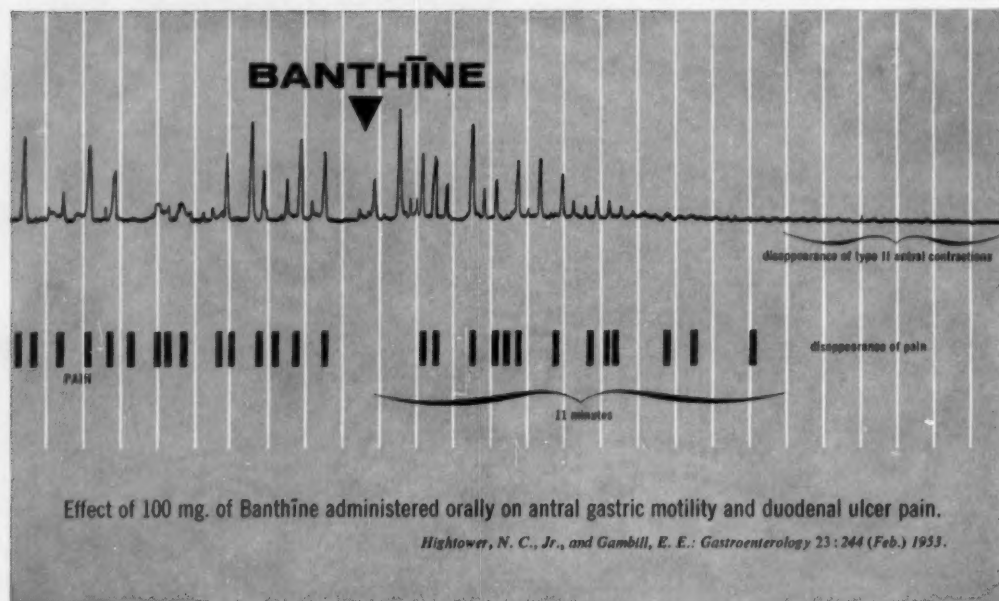
the first broad-spectrum antibiotic
available in this convenient parenteral form
for the treatment of a wide range
of infections due to susceptible organisms.

Supplied in single-dose vials. On reconstitution,
each single dose contains: Crystalline
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BANTHINE® IN PEPTIC ULCER



Hypermotility and Hyperacidity

A recent evaluation of anticholinergic therapy in peptic ulcer emphasizes the fact that now the profession has at its disposal agents that are "effective in reducing both secretory and motor activity of the stomach."

The effect on motor activity is generally more pronounced and less variable than on secretion; pain relief is usually prompt; a high degree of effectiveness is noted in ambulatory ulcer patients.

Ruffin, J. M.; Texter, E. C., Jr.; Carter, D. D., and Baylin, G. J.: *J.A.M.A.* 153:1159 (Nov. 28) 1953.

With its proved anticholinergic effectiveness, Banthine has been found extremely useful in the medical management of active peptic ulcer, whether duodenal, gastric or marginal.

The immediate increase in subjective well-being and the simplicity of the Banthine regimen assures patient cooperation. The recommended initial therapeutic dose is 50 or 100 mg. (one or two tablets) every six hours around the clock, with subsequent individual adjustment. The usual measures of diet regulation, rest and relaxation should be followed.

Banthine is effective in other conditions caused by excess parasympathetic stimulation. These include hypertrophic gastritis, acute and chronic pancreatitis, biliary dyskinesia and hyperhidrosis. Banthine is contraindicated in the presence of glaucoma and should be used with caution in the presence of severe cardiac disease or prostatic hypertrophy.

Banthine bromide (brand of methantheline bromide) is supplied in scored tablets of 50 mg. and in ampuls of 50 mg. It is accepted by the Council on Pharmacy and Chemistry of the American Medical Association. G. D. Searle & Co., Research in the Service of Medicine.

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